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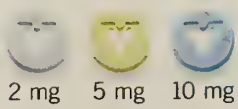

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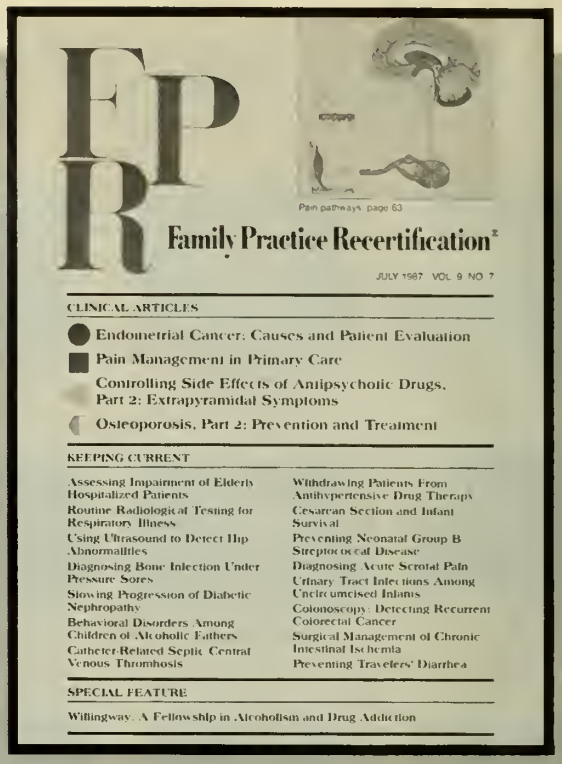
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1. Croog SH, Levine S, Testa MA, et al: The effects of antihypertensive therapy on the quality of life. N Engl J Med 314(26):1657-1664, 1986.
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CONTRAINDICATIONS: CAPOTEN is contraindicated in patients who are hypersensitive to this product.

WARNINGS: Neutropenia/Agranulocytosis – Neutropenia (< 1000/mm³) with myeloid hypoplasia has resulted from use of captopril. About half of the neutropenic patients developed systemic or oral cavity infections or other features of the syndrome of agranulocytosis. The risk of neutropenia is dependent on the clinical status of the patient:

In clinical trials in patients with hypertension who have normal renal function (serum creatinine less than 1.6 mg/dL and no collagen vascular disease), neutropenia has been seen in one patient out of over 8,600 exposed. In patients with some degree of renal failure (serum creatinine at least 1.6 mg/dL) but no collagen vascular disease, the risk in clinical trials was about 1 per 500. Doses were relatively high in these patients, particularly in view of their diminished renal function. In patients with collagen vascular diseases (e.g., systemic lupus erythematosus, scleroderma) and impaired renal function, neutropenia occurred in 3.7% of patients in clinical trials. While none of the over 750 patients in formal clinical trials of heart failure developed neutropenia, it has occurred during the subsequent clinical experience. Of reported cases, about half had serum creatinine ≥ 1.6 mg/dL and more than 75% received procainamide. In heart failure, it appears that the same risk factors for neutropenia are present.

Neutropenia has appeared usually within 3 months after starting therapy, associated with myeloid hypoplasia and frequently accompanied by erythroid hypoplasia and decreased numbers of megakaryocytes (e.g., hypoplastic bone marrow and pancytopenia); anemia and thrombocytopenia were sometimes seen. Neutrophils generally returned to normal in about 2 weeks after captopril was discontinued, and serious infections were limited to clinically complex patients. About 13% of the cases of neutropenia have ended fatally, but almost all fatalities were in patients with serious illness, having collagen vascular disease, renal failure, heart failure or immunosuppressant therapy, or a combination of these complicating factors. **Evaluation of the hypertensive or heart failure patient should always include assessment of renal function.** If captopril is used in patients with impaired renal function, white blood cell and differential counts should be evaluated prior to starting treatment and at approximately 2-week intervals for about 3 months, then periodically. In patients with collagen vascular disease or who are exposed to other drugs known to affect the white cells or immune response, particularly when there is impaired renal function, captopril should be used only after an assessment of benefit and risk, and then with caution. All patients treated with captopril should be told to report any signs of infection (e.g., sore throat, fever). If infection is suspected, perform white cell counts without delay. Since discontinuation of captopril and other drugs has generally led to prompt return of the white count to normal, upon confirmation of neutropenia (neutrophil count < 1000/mm³) withdraw captopril and closely follow the patient's course.

Proteinuria: Total urinary proteins > 1 g per day were seen in about 0.7% of patients on captopril. About 90% of affected patients had evidence of prior renal disease or received high doses (> 150 mg/day), or both. The nephrotic syndrome occurred in about one-fifth of proteinuric patients. In most cases, proteinuria subsided or cleared within 6 months whether or not captopril was continued. The BUN and creatinine were seldom altered in proteinuric patients. Since most cases of proteinuria occurred by the 8th month of therapy with captopril, patients with prior renal disease or those receiving captopril at doses > 150 mg per day, should have urinary protein estimates (dip-stick on 1st morning urine) before therapy, and periodically thereafter.

Hypotension: Excessive hypotension was rarely seen in hypertensive patients but is a possibility in severely salt/volume-depleted persons such as those treated vigorously with diuretics (see PRECAUTIONS [Drug Interactions]). In heart failure, where the blood pressure was either normal or low, transient decreases in mean blood pressure > 20% were recorded in about half of the patients. This transient hypotension may occur after any of the first several doses and is usually well tolerated, although rarely it has been associated with arrhythmia or conduction defects. A starting dose of 6.25 or 12.5 mg tid may minimize the hypotensive effect. Patients should be followed closely for the first 2 weeks of treatment and whenever the dose of captopril and/or diuretic is increased.

BECAUSE OF THE POTENTIAL FALL IN BLOOD PRESSURE IN THESE PATIENTS, THERAPY SHOULD BE STARTED UNDER VERY CLOSE MEDICAL SUPERVISION.

PRECAUTIONS: General: *Impaired Renal Function* – Hypertension – Some hypertensive patients with renal disease, particularly those with severe renal artery stenosis, have developed increases in BUN and serum creatinine. It may be necessary to reduce captopril dosage and/or discontinue diuretic. For some of these patients, normalization of blood pressure and maintenance of adequate renal perfusion may not be possible. Heart Failure – About 20% of patients develop stable elevations of BUN and serum creatinine > 20% above normal or baseline upon long-term treatment. Less than 5% of patients, generally with severe preexisting renal disease, required discontinuation due to progressively increasing creatinine. See DOSAGE AND ADMINISTRATION, ADVERSE REACTIONS [Altered Laboratory Findings]. *Valvular Stenosis* – A theoretical concern, for risk of decreased coronary perfusion, has been noted regarding vasodilator treatment in patients with aortic stenosis due to decreased afterload reduction. *Surgery/Anesthesia* – If hypotension occurs during surgery or anesthesia, and is considered due to the effects of captopril, it is correctable by volume expansion.

Drug Interactions: *Hypotension – Patients on Diuretic Therapy* – Precipitous reduction of blood pressure may occasionally occur within the 1st hour after administration of the initial of captopril dose in patients on diuretics, especially those recently placed on diuretics, and those on severe dietary salt restriction or dialysis. This possibility can be minimized by either discontinuing the diuretic or increasing the salt intake about 1 week prior to initiation of captopril therapy or by initiating therapy with small doses (6.25 or 12.5 mg). Alternatively, provide medical supervision for at least 1 hour after the initial dose.

Agents Having Vasodilator Activity – In heart failure patients, vasodilators should be administered with caution.

Agents Causing Renin Release – Captopril's effect will be augmented by antihypertensive agents that cause renin release.

Agents Affecting Sympathetic Activity – The sympathetic nervous system may be especially important in supporting blood pressure in patients receiving captopril alone or with diuretics. Beta-adrenergic blocking drugs add some further antihypertensive effect to captopril, but the overall response is less than additive. Therefore, use agents affecting sympathetic activity (e.g., ganglionic blocking agents or adrenergic neuron blocking agents) with caution.

Agents Increasing Serum Potassium – Give potassium-sparing diuretics or potassium supplements only for documented hypokalemia, and then with caution, since they may lead to a significant increase of serum potassium. Use potassium-containing salt substitutes with caution.

Inhibitors of Endogenous Prostaglandin Synthesis – Indomethacin and other nonsteroidal anti-inflammatory agents may reduce the antihypertensive effect of captopril, especially in low renin hypertension.

Drug/Laboratory Test Interaction: Captopril may cause a false-positive urine test for acetone.

Carcinogenesis, Mutagenesis and Impairment of Fertility: Two-year studies with doses of 50 to 1350 mg/kg/day in mice and rats failed to show any evidence of carcinogenic potential. Studies in rats have revealed no impairment of fertility.

Pregnancy: Category C: There are no adequate and well-controlled studies in pregnant women. Embryocidal effects and craniofacial malformations were observed in rabbits. Therefore, captopril should be used during pregnancy, or for patients likely to become pregnant, only if the potential benefit outweighs the potential risk to the fetus. Captopril crosses the human placenta.

Nursing Mothers: Captopril is secreted in human milk. Exercise caution when administering captopril to a nursing woman, and, in general, nursing should be interrupted.

Pediatric Use: Safety and effectiveness in children have not been established although there is limited experience with use of captopril in children from 2 months to 15 years of age. Dosage, on a weight basis, was comparable to that used in adults. CAPOTEN (captopril) should be used in children only if other measures for controlling blood pressure have not been effective.

ADVERSE REACTIONS: Reported incidences are based on clinical trials involving approximately 7000 patients.

Renal – About 1 of 100 patients developed proteinuria (see WARNINGS). Renal insufficiency, renal failure, polyuria, oliguria, and urinary frequency in 1 to 2 of 1000 patients.

Hematologic – Neutropenia/agranulocytosis has occurred (see WARNINGS). Anemia, thrombocytopenia, and pancytopenia have been reported.

Dermatologic – Rash, (usually maculopapular, rarely urticarial), often with pruritus, and sometimes with fever and eosinophilia, in about 4 to 7 of 100 patients (depending on renal status and dose), usually during the 1st 4 weeks of therapy. Pruritus, without rash, in about 2 of 100 patients. A reversible associated pemphigoid-like lesion, and photosensitivity, have also been reported. Angioedema of the face, mucous membranes of the mouth, or of the extremities in about 1 of 1000 patients – reversible on discontinuance of captopril therapy. One case of laryngeal edema has been reported. Flushing or pallor in 2 to 5 of 1000 patients.

Cardiovascular – Hypotension may occur; see WARNINGS and PRECAUTIONS [Drug Interactions] for discussion of hypotension on initiation of captopril therapy. Tachycardia, chest pain, and palpitations each in about 1 of 100 patients. Angina pectoris, myocardial infarction, Raynaud's syndrome, and congestive heart failure each in 2 to 3 of 1000 patients.

Dysgeusia – Approximately 2 to 4 (depending on renal status and dose) of 100 patients developed a diminution or loss of taste perception; taste impairment is reversible and usually self-limited even with continued drug use (2 to 3 months). Gastric irritation, abdominal pain, nausea, vomiting, diarrhea, anorexia, constipation, aphthous ulcers, peptic ulcer, dizziness, headache, malaise, fatigue, insomnia, dry mouth, dyspnea, cough, alopecia, paresthesias reported in about 0.5 to 2% of patients but did not appear at increased frequency compared to placebo or other treatments used in controlled trials.

Altered Laboratory Findings: Elevations of liver enzymes in a few patients although no causal relationship has been established. Rarely cholestatic jaundice, and hepatocellular injury with or without secondary cholestasis, have been reported. A transient elevation of BUN and serum creatinine may occur, especially in volume-depleted or renovascular hypertension patients. In instances of rapid reduction of longstanding or severely elevated blood pressure, the glomerular filtration rate may decrease transiently, also resulting in transient rises in serum creatinine and BUN. Small increases in serum potassium concentration frequently occur, especially in patients with renal impairment (see PRECAUTIONS).

OVERDOSAGE: Primary concern is correction of hypotension. Volume expansion with an I.V. infusion of normal saline is the treatment of choice for restoration of blood pressure. Captopril may be removed from the general circulation by hemodialysis.

DOSAGE AND ADMINISTRATION: CAPOTEN (captopril) should be taken one hour before meals. In hypertension, CAPOTEN may be dosed bid or tid. Dosage must be individualized; see DOSAGE AND ADMINISTRATION section of package insert for detailed information regarding dosage in hypertension and in heart failure. Because CAPOTEN (captopril) is excreted primarily by the kidneys, dosage adjustments are recommended for patients with impaired renal function.

Consult package insert before prescribing CAPOTEN (captopril).

HOW SUPPLIED: Available in tablets of 12.5, 25, 50, and 100 mg in bottles of 100 (25 mg and 50 mg also available in bottles of 1000), and in UNIMATIC® unit-dose packs of 100 tablets. (J3-658J)

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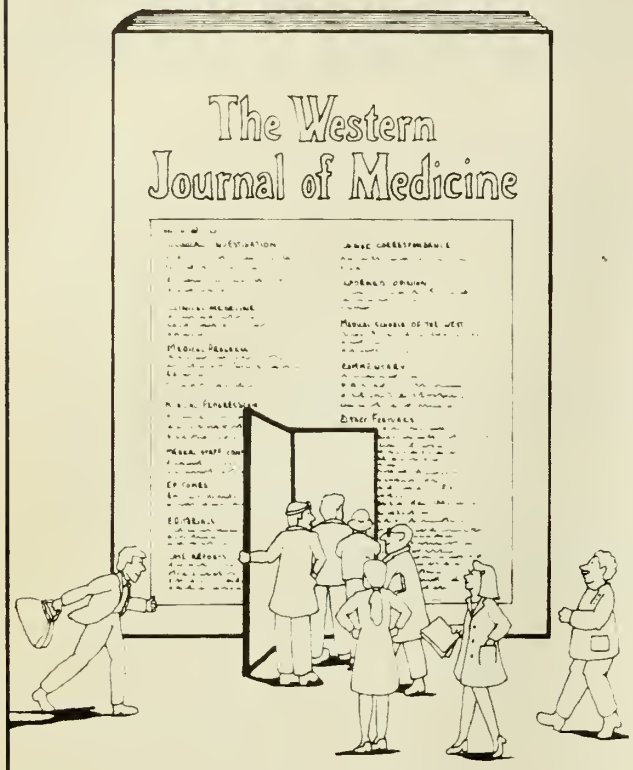

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CARAFATE
(sucralfate)

BRIEF SUMMARY

CONTRAINDICATIONS
There are no known contraindications to the use of sucralfate.

PRECAUTIONS
Duodenal ulcer is a chronic, recurrent disease. While short-term treatment with sucralfate can result in complete healing of the ulcer, a successful course of treatment with sucralfate should not be expected to alter the post-healing frequency or severity of duodenal ulceration.

Drug Interactions: Animal studies have shown that the simultaneous administration of CARAFATE with tetracycline, phenytoin, or cimetidine will result in a statistically significant reduction in the bioavailability of these agents. This interaction appears to be nonsystemic in origin, presumably resulting from these agents being bound by CARAFATE in the gastrointestinal tract. The bioavailability of these agents may be restored simply by separating the administration of these agents from that of CARAFATE by two hours. The clinical significance of these animal studies is yet to be defined.

Carcinogenesis, Mutagenesis, Impairment of Fertility: No evidence of drug-related tumorigenicity was found in chronic oral toxicity studies of 24 months' duration conducted in mice and rats at doses up to 1 gm/kg (12 times the human dose). A reproduction study in rats at doses up to 38 times the human dose did not reveal any indication of fertility impairment. Mutagenicity studies have not been conducted.

Pregnancy: Pregnancy Category B. Teratogenicity studies have been performed in mice, rats, and rabbits at doses up to 50 times the human dose and have revealed no evidence of harm to the fetus due to sucralfate. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when sucralfate is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS
Adverse reactions to sucralfate in clinical trials were minor and only rarely led to discontinuation of the drug. In studies involving over 2,500 patients, adverse effects were reported in 121 (4.7%). Constipation was the most frequent complaint (2.2%). Other adverse effects, reported in no more than one of every 350 patients, were diarrhea, nausea, gastric discomfort, indigestion, dry mouth, rash, pruritus, back pain, dizziness, sleepiness, and vertigo.

DOSAGE AND ADMINISTRATION
The recommended adult oral dosage for duodenal ulcer is 1 gm four times a day on an empty stomach.

Antacids may be prescribed as needed for relief of pain but should not be taken within one-half hour before or after sucralfate.

While healing with sucralfate may occur during the first week or two, treatment should be continued for 4 to 8 weeks unless healing has been demonstrated by x-ray or endoscopic examination.

HOW SUPPLIED
CARAFATE (sucralfate) 1-gm pink tablets are supplied in bottles of 100 and in Unit Dose Identification Paks of 100. The tablets are embossed with MARION/1712. Issued 3/84

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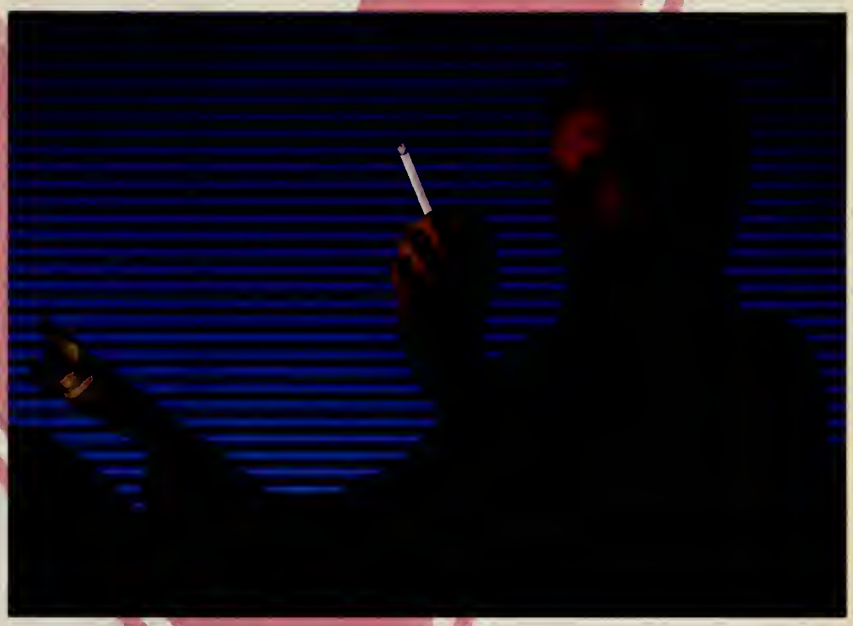
Ulcer therapy that won't yield, even to smoking



What do you do for duodenal ulcer patients who should stop smoking, but won't? Both cimetidine[1] and ranitidine[2] have been shown less effective in smokers than nonsmokers.

Choose CARAFATE® (sucralfate/Marion). Two recent studies show Carafate to be as effective in smokers as nonsmokers.[3,4] A difference further illustrated in a 283-patient study comparing sucralfate to cimetidine[5]:

Ulcer healing rates:
(at four weeks of therapy)[5]

Sucralfate:	
All patients	79.4%
Smokers	81.6%*
Cimetidine:	
All patients	76.3%
Smokers	62.5%

*Significantly greater than cimetidine smoker group ($P<.05$).

Carafate has a unique, nonsystemic mode of action that enhances the body's own ulcer healing ability and protects the damaged mucosa from further injury.

When your ulcer patient is a smoker, prescribe the ulcer medication that won't go up in smoke: safe, nonsystemic Carafate.

Nothing works like

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sucralfate/Marion

Please see adjoining page for references and brief summary of prescribing information.

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All transdermal nitroglycerin products are being marketed pending final evaluation of effectiveness by the FDA.

Please see next page for a summary of prescribing information.

Nitro-Dur® II
(nitroglycerin)
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(nitroglycerin)
Transdermal Infusion System

Thin. Translucent. Flexible.
Opens in a snap.
Available in five convenient dosage strengths: 2.5, 5, 7.5, 10 and 15 mg/24 hr.

When prescribing Nitro-Dur II, you should write your prescription using the Roman numeral designation II to identify the product. This should be followed by the appropriate dosage strength in mg/24 hours. Thus, any confusion that may arise between product names and/or dosage strengths prescribed will be avoided.

BRIEF SUMMARY

INDICATIONS AND USAGE: This drug product has been conditionally approved by the FDA for the prevention and treatment of angina pectoris due to coronary artery disease. The conditional approval reflects a determination that the drug may be marketed while further investigation of its effectiveness is undertaken. A final evaluation of the effectiveness of the product will be announced by the FDA.

CONTRAINDICATIONS: Intolerance of organic nitrate drugs, marked anemia.

WARNINGS: The NITRO-DUR II system should be used under careful clinical and/or hemodynamic monitoring in patients with acute myocardial infarction or congestive heart failure.

In terminating treatment of anginal patients, both the dosage and frequency of application must be gradually reduced over a period of 4 to 6 weeks in order to prevent sudden withdrawal reactions, which are characteristic of all vasodilators in the nitroglycerin class.

PRECAUTIONS: Symptoms of hypotension, such as faintness, weakness or dizziness, particularly orthostatic hypotension, may be due to overdosage. If during the course of treatment these symptoms occur, the dosage should be reduced or use of the product discontinued. NITRO-DUR II is not intended for use in the treatment of acute anginal attacks. For this purpose, occasional use of sublingual nitroglycerin may be necessary.

Pregnancy: Pregnancy Category C. Animal reproduction studies have not been conducted with NITRO-DUR II. It is also not known whether nitroglycerin can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Nitroglycerin should be given to a pregnant woman only if clearly needed.

Nursing Mothers: It is not known whether nitroglycerin is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when NITRO-DUR II is administered to a nursing woman.

ADVERSE REACTIONS: Transient headache is the most common side effect, especially when higher doses of the drug are administered. Headaches should be treated with mild analgesics while continuing NITRO-DUR II therapy. If headache persists, the NITRO-DUR II dosage should be reduced or use of the product discontinued.

Adverse reactions reported less frequently include hypotension, increased heart rate, faintness, flushing, dizziness, nausea, vomiting, and dermatitis. Except for dermatitis, these symptoms are attributed to the pharmacologic effects of nitroglycerin. However, they may be symptoms of overdosage. When they persist, the NITRO-DUR II dosage should be reduced or use of the product discontinued.

CAUTION: Federal law prohibits dispensing without prescription. For complete prescribing information, please see package insert.

EDP #I030150 Revised 0585

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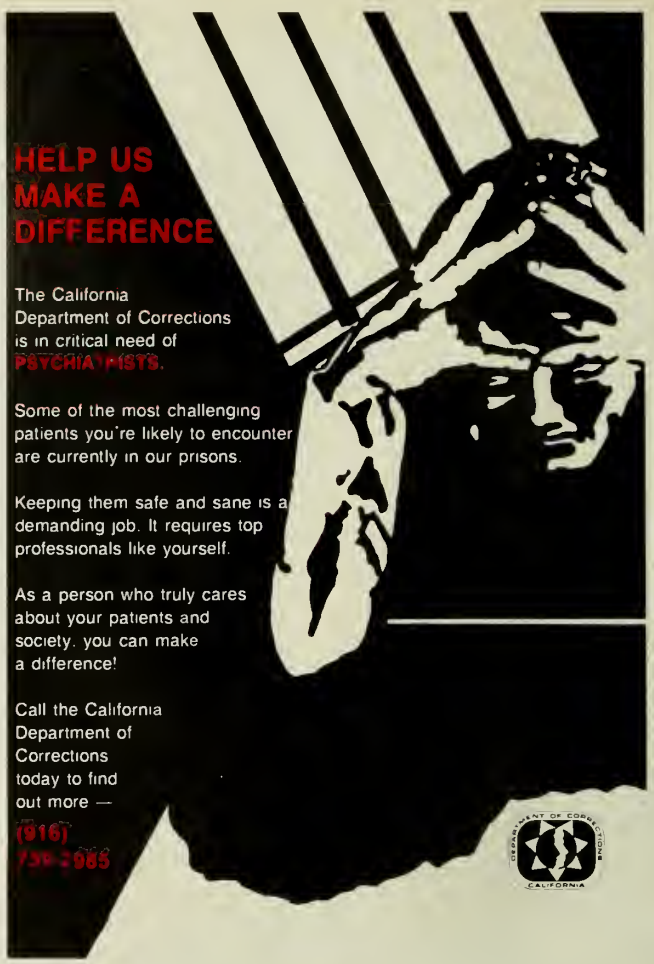

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L-K244-1-87

Routine VI-FLOR* supplementation

to help you guard appropriate patients against caries risk and nutritional risk.

INDICATIONS AND USAGE: Prophylaxis of vitamin deficiencies and dental caries in children and adults when fluoride of water supply does not exceed 0.7 ppm.[1,2,3] And, in the case of TRI-VI-FLOR* 0.25 mg Drops with Iron and POLY-VI-FLOR* Drops and Chewable Tablets with Iron, prophylaxis against iron deficiencies. Note: VI-FLOR Drops do not contain folic acid because the vitamin is not stable in liquid form.

PRECAUTIONS: Do not exceed recommended dose or give concurrently with other medications containing significant amounts of fluoride. Prolonged excessive fluoride intake may cause dental fluorosis. All VI-FLOR* with Iron products: as with all products containing iron, parents should be warned against excessive dosage. The bottle should be kept out of reach of children.

Keep all VI-FLOR with Iron products tightly closed and away from direct light.

VI-FLOR Drops should be dispensed in the original plastic container, since contact with glass leads to instability and precipitation.

ADVERSE REACTIONS: Allergic rash has rarely been reported.

DOSAGE AND ADMINISTRATION:
Supplemeotal Fluoride Dosage Schedule (mg/day)*

Age	Concentratioo of Fluoride io Drinkiog Water (ppm)		
	<0.3	0.3-0.7	>0.7
2-wk-2 yr**	0.25	0	0
2-3 yr	0.5	0.25	0
3-16 yr	1.0	0.5	0

*From the American Academy of Pediatrics Committee on Nutrition statement. Fluoride Supplementation: Revised Dosage Schedule. *Pediatrics* 63(1):150-152, 1979.
**The Committee favors initiating fluoride supplementation shortly after birth in breast-fed infants (0.25 mg F/day). In formula-fed infants, fluoride supplementation should be according to the fluoride content of the water used to prepare formula

PRODUCT	FORM	SIZE	FLUORIDE mg/dose
POLY-VI-FLOR 0.25 mg	Drops	50 ml Bottle	0.25
POLY-VI-FLOR 0.25 mg with Iron	Drops	50 ml Bottle	0.25
POLY-VI-FLOR 0.25 mg	Tablets	Bottle of 100	0.25
POLY-VI-FLOR 0.25 mg with Iron	Tablets	Bottle of 100	0.25
POLY-VI-FLOR 0.5 mg	Drops	50 ml Bottle	0.5
POLY-VI-FLOR 0.5 mg with Iron	Drops	50 ml Bottle	0.5
POLY-VI-FLOR 0.5 mg	Tablets	Bottle of 100	0.5
POLY-VI-FLOR 0.5 mg with Iron	Tablets	Bottle of 100	0.5
POLY-VI-FLOR 1.0 mg	Tablets	Bottle of 100	1.0
POLY-VI-FLOR 1.0 mg with Iron	Tablets	Bottle of 100	1.0
TRI-VI-FLOR 0.25 mg	Drops	50 ml Bottle	0.25
TRI-VI-FLOR 0.25 mg with Iron	Drops	50 ml Bottle	0.25
TRI-VI-FLOR 0.5 mg	Drops	50 ml Bottle	0.5
TRI-VI-FLOR 1.0 mg	Tablets	Bottle of 100	1.0

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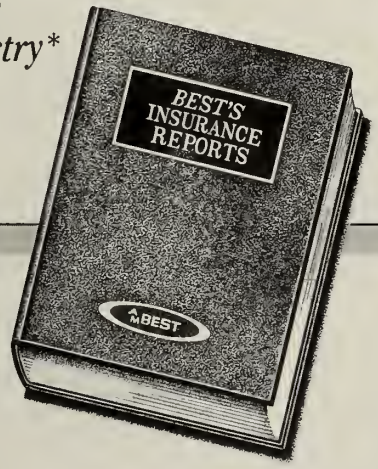

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IN HYPERTENSION

resistance in the elderly[1]

- ☐ Effective blood pressure control
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Contraindicated in bronchial asthma, overt cardiac failure, greater-than-first-degree heart block, cardiogenic shock, and severe bradycardia.

See next page for references and Brief Summary of Product Information, which includes a listing of reported adverse reactions.

TRANDATE® *b.i.d.*

labetalol HCl/Glaxo *100 mg/200 mg tablets*

Because it also vasodilates

References: 1. Holtzman JL, Finley O, Johnson B, et al. The effects of single-dose atenolol, labetalol, and propranolol on cardiac and vascular function. *Clin Pharmacol Ther* 1986;40:268-273 2. Oue OL, Giguere GC, Plachetka JR. Postmarketing comparison of labetalol and propranolol in hypertensive patients. *Clin Ther* 1986;8(6):624-631. 3. Burris JF, Goldstein J, Zager PG, et al. Comparative tolerability of labetalol versus propranolol, atenolol, pindolol, metoprolol, and nadolol. *J Clin Hypertens* 1986;3:1-9 4. Erb RJ, Plachetka JR. Thermographic evaluation of the peripheral vascular effects of labetalol and propranolol. *Curr Ther Res* 1985;28(1):68-73.

TRANDATE® Tablets
(labetalol hydrochloride)

BRIEF SUMMARY OF PRODUCT INFORMATION

The following is a brief summary only. Before prescribing, see complete prescribing information in TRANDATE® Tablets product labeling.

INDICATIONS AND USAGE: TRANDATE® Tablets are indicated in the management of hypertension. TRANDATE Tablets may be used alone or in combination with other antihypertensive agents, especially thiazide and loop diuretics.

CONTRAINDICATIONS: TRANDATE® Tablets are contraindicated in bronchial asthma, overt cardiac failure, greater-than-first-degree heart block, cardiogenic shock, and severe bradycardia (see **WARNINGS**).

WARNINGS: Cardiac Failure: Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure. Beta-blockade carries a potential hazard of further depressing myocardial contractility and precipitating more severe failure. Although beta-blockers should be avoided in overt congestive heart failure, if necessary labetalol HCl can be used with caution in patients with a history of heart failure who are well compensated. Congestive heart failure has been observed in patients receiving labetalol HCl. Labetalol HCl does not abolish the inotropic action of digitalis on heart muscle.

In Patients Without a History of Cardiac Failure: In patients with latent cardiac insufficiency, continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or be given a diuretic, and the response should be observed closely. If cardiac failure continues despite adequate digitalization and diuretic, TRANDATE® therapy should be withdrawn (gradually, if possible).

Exacerbation of Ischemic Heart Disease Following Abrupt Withdrawal: Angina pectoris has not been reported upon labetalol HCl discontinuation. However, hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy; exacerbation of angina and, in some cases, myocardial infarction have occurred after *abrupt* discontinuation of such therapy. When discontinuing chronically administered TRANDATE, particularly in patients with ischemic heart disease, the dosage should be gradually reduced over a period of one to two weeks and the patient should be carefully monitored. If angina markedly worsens or acute coronary insufficiency develops, TRANDATE administration should be reinstituted promptly, at least temporarily, and other measures appropriate for the management of unstable angina should be taken. Patients should be warned against interruption or discontinuation of therapy without the physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue TRANDATE therapy abruptly even in patients treated only for hypertension.

Nonallergic Bronchospasm (eg, Chronic Bronchitis and Emphysema): Patients with bronchospastic disease should, in general, not receive beta-blockers. TRANDATE may be used with caution, however, in patients who do not respond to, or cannot tolerate, other antihypertensive agents. It is prudent, if TRANDATE is used, to use the smallest effective dose, so that inhibition of endogenous or exogenous beta-agonists is minimized.

Pheochromocytoma: Labetalol HCl has been shown to be effective in lowering blood pressure and relieving symptoms in patients with pheochromocytoma. However, paradoxical hypertensive responses have been reported in a few patients with this tumor; therefore, use caution when administering labetalol HCl to patients with pheochromocytoma.

Diabetes Mellitus and Hypoglycemia: Beta-adrenergic blockade may prevent the appearance of premonitory signs and symptoms (eg, tachycardia) of acute hypoglycemia. This is especially important with labile diabetics. Beta-blockade also reduces the release of insulin in response to hyperglycemia; it may therefore be necessary to adjust the dose of antidiabetic drugs.

Major Surgery: The necessity or desirability of withdrawing beta-blocking therapy prior to major surgery is controversial. Protracted severe hypotension and difficulty in restarting or maintaining a heartbeat have been reported with beta-blockers. The effect of labetalol HCl's alpha-adrenergic activity has not been evaluated in this setting.

A synergism between labetalol HCl and halothane anesthesia has been shown (see **Drug Interactions** under **PRECAUTIONS**).

PRECAUTIONS: General: ***Impaired Hepatic Function:*** TRANDATE® Tablets should be used with caution in patients with impaired hepatic function since metabolism of the drug may be diminished.

Jaundice or Hepatic Dysfunction: On rare occasions, labetalol HCl has been associated with jaundice (both hepatic and cholestatic). It is therefore recommended that treatment with labetalol HCl be stopped immediately should a patient develop jaundice or laboratory evidence of liver injury. Both have been shown to be reversible on stopping therapy.

Information for Patients: As with all drugs with beta-blocking activity, certain advice to patients being treated with labetalol HCl is warranted. This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects. While no incidence of the abrupt withdrawal phenomenon (exacerbation of angina pectoris) has been reported with labetalol HCl, dosing with TRANDATE Tablets should not be interrupted or discontinued without a physician's advice. Patients being treated with TRANDATE Tablets should consult a physician at any sign of impending cardiac failure. Also, transient scalp tingling may occur, usually when treatment with TRANDATE Tablets is initiated (see **ADVERSE REACTIONS**).

Laboratory Tests: As with any new drug given over prolonged periods, laboratory parameters should be observed over regular intervals. In patients with concomitant illnesses, such as impaired renal function, appropriate tests should be done to monitor these conditions.

Drug Interactions: In one survey, 2.3% of patients taking labetalol HCl in combination with tricyclic antidepressants experienced tremor as compared to 0.7% reported to occur with labetalol HCl alone. The contribution of each of the treatments to this adverse reaction is unknown, but the possibility of a drug interaction cannot be excluded.

Drugs possessing beta-blocking properties can blunt the bronchodilator effect of beta-receptor agonist drugs in patients with bronchospasm; therefore, doses greater than the normal antiasthmatic dose of beta-agonist bronchodilator drugs may be required.

Cimetidine has been shown to increase the bioavailability of labetalol HCl. Since this could be explained either by enhanced absorption or by an alteration of hepatic metabolism of labetalol HCl, special care should be used in establishing the dose required for blood pressure control in such patients.

Synergism has been shown between halothane anesthesia and intravenously administered labetalol HCl. During controlled hypotensive anesthesia using labetalol HCl in association with halothane, high concentrations (3% or above) of halothane should not be used because the degree of hypotension will be increased and because of the possibility of a large reduction in cardiac output and an increase in central venous pressure. The anesthesiologist should be informed when a patient is receiving labetalol HCl.

Labetalol HCl blunts the reflex tachycardia produced by nitroglycerin without preventing its hypotensive effect. If labetalol HCl is used with nitroglycerin in patients with angina pectoris, additional antihypertensive effects may occur.

Drug/Laboratory Test Interactions: The presence of a metabolite of labetalol in the urine may result in falsely increased levels of urinary catecholamines when measured by a nonspecific trihydroxyindole (THI) reaction. In screening patients suspected of having a pheochromocytoma and being treated with labetalol HCl, specific radioenzymatic or high performance liquid chromatography assay techniques should be used to determine levels of catecholamines or their metabolites.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term oral dosing studies with labetalol HCl for 18 months in mice and for two years in rats showed no evidence of carcinogenesis. Studies with labetalol HCl using dominant lethal assays in rats and mice and exposing microorganisms according to modified Ames tests showed no evidence of mutagenesis.

Pregnancy: ***Teratogenic Effects: Pregnancy Category C:*** Teratogenic studies have been performed with

TRANDATE® Tablets (labetalol hydrochloride)

labetalol in rats and rabbits at oral doses up to approximately six and four times the maximum recommended human dose (MRHD), respectively. No reproducible evidence of fetal malformations was observed. Increased fetal resorptions were seen in both species at doses approximating the MRHD. There are no adequate and well-controlled studies in pregnant women. Labetalol should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects: Infants of mothers who were treated with labetalol HCl during pregnancy did not appear to be adversely affected by the drug. Oral administration of labetalol to rats during late gestation through weaning at doses of two to four times the MRHD caused a decrease in neonatal survival.

Labor and Delivery: Labetalol HCl given to pregnant women with hypertension did not appear to affect the usual course of labor and delivery.

Nursing Mothers: Small amounts of labetalol (approximately 0.004% of the maternal dose) are excreted in human milk. Caution should be exercised when TRANDATE Tablets are administered to a nursing woman.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: Most adverse effects are mild, transient, and occur early in the course of treatment. In controlled clinical trials of three to four months' duration, discontinuation of TRANDATE® Tablets due to one or more adverse effects was required in 7% of all patients. In these same trials, beta-blocker control agents led to discontinuation in 8% to 10% of patients, and a centrally acting alpha-agonist in 30% of patients.

The following adverse reactions were derived from multi-center, controlled clinical trials over treatment periods of three and four months. The rates, which ranged from less than 1% to 5% except as otherwise noted, are based on adverse reactions considered probably drug-related by the investigator. If all reports are considered, the rates are somewhat higher (eg, dizziness, 20%; nausea, 14%; fatigue, 11%).

Body as a Whole: Fatigue, asthenia, and headache.

Gastrointestinal: Nausea (6%), vomiting, dyspepsia, diarrhea, and taste distortion.

Central and Peripheral Nervous Systems: Dizziness (11%), paresthesia, and drowsiness.

Autonomic Nervous System: Nasal stuffiness, ejaculation failure, impotence, and increased sweating.

Cardiovascular: Edema and postural hypotension.

Respiratory: Dyspnea.

Skin: Rash.

Special Senses: Vision abnormality and vertigo.

The adverse effects were reported spontaneously and are representative of the incidence of adverse effects that may be observed in a properly selected hypertensive patient population, ie, a group excluding patients with bronchospastic disease, overt congestive heart failure, or other contraindications to beta-blocker therapy.

Clinical trials also included studies utilizing daily doses up to 2,400 mg in more severely hypertensive patients. The US therapeutic trials data base for adverse reactions that are clearly or possibly dose-related shows that the following side effects increased with increasing dose: dizziness, fatigue, nausea, vomiting, dyspepsia, paresthesia, nasal stuffiness, ejaculation failure, impotence, and edema.

In addition, a number of other less common adverse events have been reported in clinical trials or the literature:

Cardiovascular: Postural hypotension, including rarely, syncope.

Central and Peripheral Nervous Systems: Paresthesias, most frequently described as scalp tingling. In most cases, it was mild, transient, and usually occurred at the beginning of treatment.

Collagen Disorders: Systemic lupus erythematosus; positive antinuclear factor (ANF).

Eyes: Dry eyes.

Immunological System: Antimitochondrial antibodies.

Liver and Biliary System: Cholestasis with or without jaundice.

Musculoskeletal System: Muscle cramps; toxic myopathy.

Respiratory System: Bronchospasm.

Skin and Appendages: Rashes of various types, such as generalized maculopapular, lichenoid, urticarial, bullous lichen planus, psoriaform, and facial erythema; Peyronie's disease; reversible alopecia.

Urinary System: Difficulty in micturition, including acute urinary bladder retention.

Following approval for marketing in the United Kingdom, a monitored release survey involving approximately 6,800 patients was conducted for further safety and efficacy evaluation of this product. Results of this survey indicate that the type, severity, and incidence of adverse effects were comparable to those cited above.

Potential Adverse Effects: In addition, other adverse effects not listed above have been reported with other beta-adrenergic blocking agents.

Central Nervous System: Reversible mental depression progressing to catatonia, an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance or neuropsychometrics.

Cardiovascular: Intensification of AV block (see **CONTRAINDICATIONS**).

Allergic: Fever combined with aching and sore throat; laryngospasm; respiratory distress.

Hematologic: Agranulocytosis; thrombocytopenic or nonthrombocytopenic purpura.

Gastrointestinal: Mesenteric artery thrombosis; ischemic colitis.

The oculomucocutaneous syndrome associated with the beta-blocker practolol has not been reported with labetalol HCl.

Clinical Laboratory Tests: There have been reversible increases of serum transaminases in 4% of patients treated with labetalol HCl and tested, and more rarely, reversible increases in blood urea.

OVERDOSAGE: Information concerning possible overdosage and its treatment appears in the full prescribing information.

DOSAGE AND ADMINISTRATION: DOSAGE MUST BE INDIVIDUALIZED. The recommended *initial* dosage is 100 mg *twice* daily whether used alone or added to a diuretic regimen. After two or three days, using standing blood pressure as an indicator, dosage may be titrated in increments of 100 mg bid every two or three days. The usual *maintenance* dosage of labetalol HCl is between 200 and 400 mg *twice* daily. Before use, see complete prescribing information for dosage details.

HOW SUPPLIED: TRANDATE® Tablets, 100 mg, light orange, round, scored, film-coated tablets engraved on one side with "TRANDATE 100 GLAXO," bottles of 100 (NDC 0173-0346-43) and 500 (NDC 0173-0346-44) and unit dose packs of 100 tablets (NDC 0173-0346-47).

TRANDATE Tablets, 200 mg, white, round, scored, film-coated tablets engraved on one side with "TRANDATE 200 GLAXO," bottles of 100 (NDC 0173-0347-43) and 500 (NDC 0173-0347-44) and unit dose packs of 100 tablets (NDC 0173-0347-47).

TRANDATE Tablets, 300 mg, peach, round, scored, film-coated tablets engraved on one side with "TRANDATE 300 GLAXO," bottles of 100 (NDC 0173-0348-43) and 500 (NDC 0173-0348-44) and unit dose packs of 100 tablets (NDC 0173-0348-47).

TRANDATE Tablets should be stored between 2° and 30°C (36° and 86°F). TRANDATE Tablets in the unit dose boxes should be protected from excessive moisture.

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September 1986

Glaxo

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Research Triangle Park, NC 27709

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The Western Journal of Medicine

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★ Affiliated Clinical Investigation Societies: the Western Association of Physicians; the Western Society for Clinical Investigation; the Western Section, American Federation for Clinical Research; the Western Society for Pediatric Research; the Western Region, Society for Investigative Dermatology.

The portrait of anxiety

Upjohn The Upjohn Company
Kalamazoo, Michigan 49001 USA

Please see adjacent page for brief summary of prescribing information.

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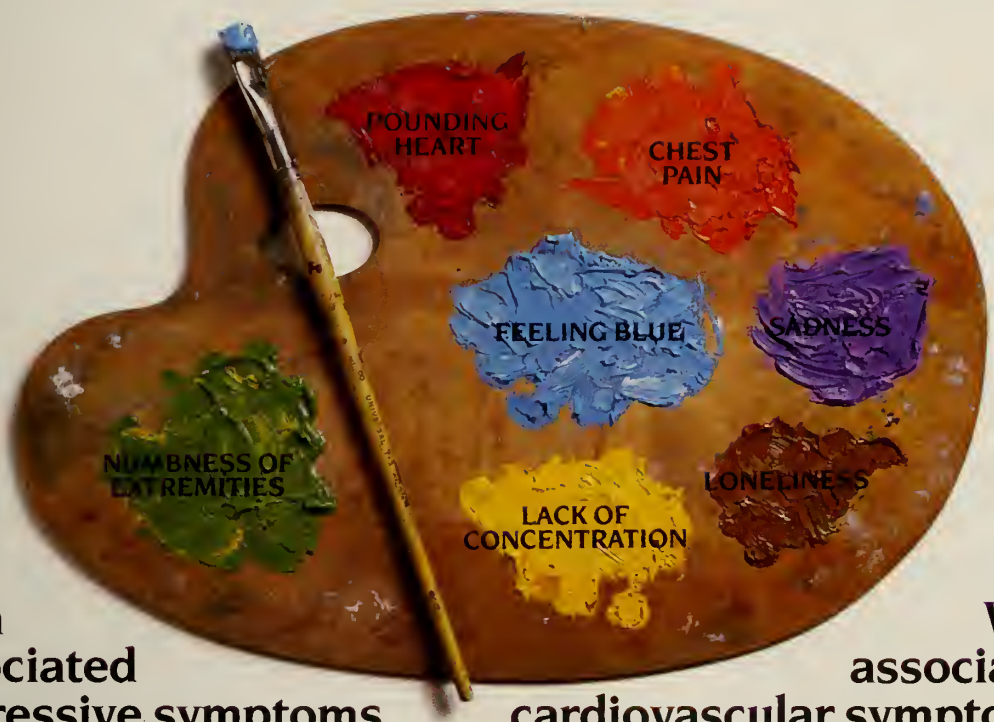
is often complicated



With associated depressive symptoms.

In double-blind, four-week clinical trials in 632 patients with moderate to severe anxiety, therapy with XANAX was compared with placebo.

XANAX was significantly more effective ($P<.001$) than placebo in relieving the anxiety, with over half of the patients showing marked to moderate improvement by the first evaluation period (one week).

In addition, over 70% of these patients experienced associated moderate to severe depressed mood. XANAX was shown to be significantly more effective ($P<.014$) than placebo in improving the associated depressed mood.

With associated cardiovascular symptoms.

Almost 60% of patients in the study had anxiety with associated cardiovascular symptoms even though cardiovascular disease had been ruled out. XANAX was shown to effectively relieve anxiety including the associated cardiovascular symptoms.

XANAX, the first of a unique class—the triazolobenzodiazepines.

- *Well tolerated*—Side effects, if they occur, are generally observed at the beginning of therapy and usually disappear with continued medication. Drowsiness and light-headedness were the most commonly reported adverse reactions.
- *Sustained efficacy*—No reported increase in dosage during 16-week clinical study, once an appropriate dosage was achieved. Since long-term effectiveness of XANAX has not been established, it is recommended that it not be used for longer than 16 weeks.
- *Simple dosage*—0.25 to 0.5 mg t.i.d.

TABLETS 0.25, 0.5 & 1 MG

Xanax®

alprazolam IV

for the relief of complicated anxiety

XANAX® Tablets
(alprazolam) C

CONTRAINDICATIONS
Patients with sensitivity to this drug or other benzodiazepines and in acute narrow angle glaucoma.

WARNINGS
Not of value in psychotic patients. Caution patients against hazardous occupations requiring complete mental alertness and about the simultaneous ingestion of alcohol and other CNS depressant drugs.

Benzodiazepines can cause fetal harm in pregnant women. Warn patients of the potential hazard to the fetus. Avoid during the first trimester.

PRECAUTIONS
General: The dosage of XANAX Tablets should be reduced or withdrawn gradually, since withdrawal seizures have been reported upon abrupt withdrawal. If XANAX is combined with other psychotropics or anticonvulsant drugs, consider drug potentiation (see Drug Interaction section). Exercise the usual precautions regarding size of the prescription for depressed or suicidal patients. In elderly and debilitated patients, use the lowest possible dosage (see Dosage and Administration). Observe the usual precautions in treating patients with impaired renal or hepatic function.

Information for Patients: Alert patients about: (a) consumption of alcohol and drugs, (b) possible fetal abnormalities, (c) operating machinery or driving, (d) not increasing dose of the drug due to risk of dependence, (e) not stopping the drug abruptly. *Laboratory Tests:* Not ordinarily required in otherwise healthy patients. *Drug Interactions:* Additive CNS depressant effects with other psychotropics, anticonvulsants, antihistamines, ethanol and other CNS depressants. Pharmacokinetic interactions with other drugs, e.g., cimetidine, have been reported. *Drug/Laboratory Test Interactions:* No consistent pattern for a drug or test. *Carcinogenesis, Mutagenesis, Impairment of Fertility:* No carcinogenic potential or impairment of fertility in rats. *Pregnancy:* See Warnings. *Nonteratogenic Effects:* The child born of a mother on benzodiazepines may be at some risk for withdrawal symptoms and neonatal flaccidity. *Labor and Delivery:* No established use. *Nursing Mothers:* Benzodiazepines are excreted in human milk. Women on XANAX should not nurse. *Pediatric Use:* Safety and effectiveness in children below the age of 18 have not been established.

ADVERSE REACTIONS
Side effects are generally observed at the beginning of therapy and usually disappear with continued medication. In the usual patient, the most frequent side effects are likely to be an extension of the pharmacologic activity of XANAX, e.g., drowsiness or lightheadedness.

Central nervous system: Drowsiness, lightheadedness, depression, headache, confusion, insomnia, nervousness, syncope, dizziness, akathisia, and tiredness/sleepiness. *Gastrointestinal:* Dry mouth, constipation, diarrhea, nausea/vomiting, and increased salivation. *Cardiovascular:* Tachycardia/palpitations, and hypotension. *Sensory:* Blurred vision. *Musculoskeletal:* Rigidity and tremor. *Cutaneous:* Dermatitis/allergy. *Other side effects:* Nasal congestion, weight gain, and weight loss.

Withdrawal seizures have been reported upon rapid decrease or abrupt discontinuation of XANAX. (See Precautions.)

In addition, the following adverse events have been reported with the use of benzodiazepines: dystonia, irritability, concentration difficulties, anorexia, transient amnesia or memory impairment, loss of coordination, fatigue, sedation, slurred speech, jaundice, musculoskeletal weakness, pruritus, diplopia, dysarthria, changes in libido, menstrual irregularities, incontinence and urinary retention.

Paradoxical reactions such as stimulation, agitation, increased muscle spasticity, sleep disturbances, and hallucinations may occur. Should these occur, discontinue the drug.

During prolonged treatment, periodic blood counts, urinalysis, and blood chemistry analysis are advisable. Minor EEG changes, of unknown significance, have been observed.

DRUG ABUSE AND DEPENDENCE
Physical and Psychological Dependence: Withdrawal symptoms have occurred following abrupt discontinuance of benzodiazepines. Withdrawal seizures have occurred upon rapid decrease or abrupt discontinuation of therapy. In all patients, dosage should be gradually tapered under close supervision. Patients with a history of seizures or epilepsy should not be abruptly withdrawn from XANAX. Addiction-prone individuals should be under careful surveillance. *Controlled Substance Class:* XANAX is a controlled substance and has been assigned to schedule IV.

OVERDOSAGE
Manifestations include somnolence, confusion, impaired coordination, diminished reflexes and coma. No delayed reactions have been reported.

DOSAGE AND ADMINISTRATION
Dosage should be individualized.

The usual starting dose is 0.25 to 0.5 mg, t.i.d. Maximum total daily dose is 4 mg. In the elderly or debilitated, the usual starting dose is 0.25 mg, two or three times daily. Reduce dosage gradually when terminating therapy, by no more than 0.5 milligram every three days.

HOW SUPPLIED
XANAX Tablets are available as 0.25 mg, 0.5 mg, and 1 mg tablets.

Caution: Federal law prohibits dispensing without prescription. B-5-S

Upjohn THE UPJOHN COMPANY J-7384
Kalamazoo, Michigan 49001 USA February 1987

Books Received

Books received by THE WESTERN JOURNAL OF MEDICINE *are acknowledged in this column. Selections will be made for more extensive review in the interest of readers as space permits.*

ACUTE MEDICAL PROBLEMS IN THE POSTOPERATIVE PATIENT—Edited by George A. Porter, MD, Professor and Chairman, Department of Medicine, Oregon Health Sciences University, Portland. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1987. 216 pages, $24 (paperback).

ADVANCES IN UROLOGIC ONCOLOGY—Volume 1—GENERAL PERSPECTIVES—Edited by Richard D. Williams, MD, Professor and Chairman, Department of Urology, University of Iowa College of Medicine, Iowa City. Macmillan Publishing Co, 866 Third Ave, New York, NY 10022, 1987. 212 pages, $37.50.

THE CALIFORNIA PROFESSIONAL CORPORATION HANDBOOK—Third Edition—Anthony Mancuso. Nolo Press, 950 Parker St, Berkeley, CA 94710, 1987. 224 pages, $29.95 (paperback).

THE CARE OF PATIENTS—PERSPECTIVES AND PRACTICES—Revised Edition—Mack Lipkin, MD, Clinical Professor of Medicine, University of North Carolina Medical School, Chapel Hill. Yale University Press, 92A Yale University, New Haven, CT 06520, 1987. 228 pages, price not given (paperback).

COMMUNITY-ORIENTED PRIMARY CARE: FROM PRINCIPLE TO PRACTICE—Edited by Paul A. Nutting, MD. US Department of Health and Human Services, Superintendent of Documents, US Government Printing Office, Washington, DC 20402, 1987. 539 pages, $16 (paperback).

CPT & HCPCS CODING FOR OPTIMAL REIMBURSEMENT—Gary M. Knaus. Medical Administration Publications, PO Box 9268, Downers Grove, IL 60515, 1987. 267 pages, $39.95 (paperback).

DIAGNOSTIC RECOGNITION OF GENETIC DISEASE—William L. Nyhan, MD, PhD, Professor and Chairman, Department of Pediatrics, University of California, San Diego, and Nadia A. Sakati, MD, Geneticist and Endocrinologist, King Faisal Hospital and Research Center, Riyadh, Saudi Arabia. Lea & Febinger, 600 Washington Square, Philadelphia, PA 19106-4198, 1987. 720 pages, $75.

THE ECG IN ANESTHESIA AND CRITICAL CARE—Edited by Daniel M. Thys, MD, Associate Professor and Director, Division of Cardiothoracic Anesthesia, and Joel A. Kaplan, MD, Professor and Chairman, Department of Anesthesiology, Mount Sinai School of Medicine of the City University of New York. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1987, 257 pages, $24 (paperback).

ELECTROMYOGRAPHY IN CLINICAL PRACTICE—ELECTRODIAGNOSTIC ASPECTS OF NEUROMUSCULAR DISEASE—2nd Edition—Michael J. Aminoff, MD, FRCP, Professor, Department of Neurology, University of California, San Francisco, School of Medicine, and Director, Clinical Neurophysiology Laboratories, and Attending Physician, Department of Neurology, University of California Medical Center, San Francisco. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1987. 347 pages, $54.

FINANCIAL PLANNING WORKBOOK FOR PHYSICIANS—Steven B. Enright, CFP. Medical Economics Books, Oradell, NJ 07649, 1987. 225 pages, $28.95 (paperback).

GALLBLADDER AND BILE DUCT IMAGING—A CLINICAL RADIOLOGIC APPROACH—Robert K. Zeman, MD, Professor of Radiology, Georgetown University School of Medicine, and Clinical Director of Diagnostic Radiology, Georgetown University Hospital, Washington, and Morton I. Burrell, MD, Professor of Radiology, Yale University School of Medicine, and Director of Gastrointestinal Radiology, Yale-New Haven Hospital, Connecticut. Churchill Livingstone Inc. 1560 Broadway, New York, NY 10036, 1987. 777 pages, $160.

GERIATRIC AMBULATORY AND INSTITUTIONAL CARE—James D. Lomax, MD, Director, Department of Family Practice, Long Island College Hospital, Brooklyn, New York. Ishiyaku EuroAmerica, Inc, 11559 Rock Island Ct, Maryland Heights, MO 63043, 1987. 209 pages, $27.50 (paperback).

HANDBOOK OF HEAD AND NECK IMAGING—June M. Unger, MD, Professor of Radiology, University of Wisconsin Clinical Science Center, Madison; Clinical Professor of Radiology, Medical College of Wisconsin; and Consultant in Radiology, Clement J. Zablocki Veterans Administration Medical Center, Milwaukee. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1987. 225 pages, $55.

HANDBOOK OF OFFICE & AMBULATORY GYNECOLOGIC SURGERY—Edited by Philip D. Darney, MD, Associate Professor in Residence, Department of Obstetrics, Gynecology, and Reproductive Sciences, University of California, San Francisco, School of Medicine. Medical Economics Books, Oradell, NJ 07649, 1987. 220 pages, $24.95 (paperback).

HEALTH PROBLEMS OF HEALTH-CARE WORKERS—Volume 2 in Occupational Medicine: State of the Art Reviews—Edited by Edward A. Emmett, MD, Professor and Director, Division of Occupational Medicine, School of Hygiene and Public Health, The Johns Hopkins University, Baltimore. Hanley & Belfus, Inc, 210 S 13th St, Philadelphia, PA 19107, 1987. 649 pages, $28.

THE HUMAN VOCAL TRACT: ANATOMY, FUNCTION, DEVELOPMENT, AND EVOLUTION—Edmund S. Crelin, PhD, DSc, Professor and Chief, Section of Human Anatomy and Development, Departments of Surgery and Orthopedics and Rehabilitation, Yale University School of Medicine, and Chairman, Human Growth and Development Study Unit, Yale-New Haven Medical Center, Connecticut. Vantage Press, 516 W 34th St, New York, NY 10001, 1987. 262 pages, $25.

MANUAL OF ANESTHESIA FOR EMERGENCY SURGERY—Edited by Judith Donegan, MD, PhD, Professor of Anesthesia and Neurosurgery, Department of Anesthesia, University of California, San Francisco, School of Medicine. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1987. 373 pages, $29 (paperback).

(Continued on Page 30)

INFORMATION FOR AUTHORS

Submitting Manuscripts

Manuscripts for consideration should be sent to the editor, Malcolm S. M. Watts, MD, PO Box 7602, San Francisco, California 94120-7602. The transmittal letter should designate one person as correspondent and include complete address, with ZIP code and telephone number.

In view of *The Copyright Revision Act of 1976*, transmittal letters should contain the following language: "In consideration for reviewing and editing my submission, the author(s) undersigned hereby transfers, assigns, or otherwise conveys all copyright ownership to THE WESTERN JOURNAL OF MEDICINE in the event that such work is published by the journal." This statement should be signed by *all* authors.

Authors are urged to seek clarity and succinctness in all manuscripts regardless of subject matter or format and to give close attention to syntax, grammar, and spelling.

Clinical Investigation Section

Articles that authors wish to have considered for the Clinical Investigation section should be so designated in the transmittal letter. The type of articles appropriate for this section are those that describe experimental work in humans that extensively and prospectively examines scientific hypotheses relating to disease. An article describing a single case report will not normally be considered appropriate for this section.

Preparing Manuscripts

The original manuscript and *two* copies should be submitted on heavy bond paper (8½ by 11 inches, *not* erasable), typed *double-spaced throughout* (including legends, tables, and references) on one side of the paper, with 1½-inch margins. Articles should not exceed 3,000 words (less than 15 text pages typed double-spaced). Under exceptional circumstances only will articles longer than 4,000 words be published. Pages should be numbered consecutively, beginning with the title page. Manuscripts produced with a dot-matrix printer are ordinarily not acceptable.

Style

Abbreviations. Use of abbreviations should be minimized. If they are necessary, abbreviations should be spelled out at first mention, with the abbreviation itself immediately following in parentheses.

Weights and measures. Use Système International (SI) units throughout the manuscript. Provide metric equivalents for all SI units; they will be noted parenthetically in the published text.

Temperatures. Temperature readings should be given first in Celsius, followed by the Fahrenheit equivalent in parentheses.

Drug names. If the trade name of a drug is used, the generic name, including salt or ester, should be given first, followed by the trade name in parentheses. Trade names are capitalized, generic names are not.

Title Page

Titles are best when brief and concise. The title page should include the full name of the author(s), with degrees, academic or professional titles, complete addresses, and any institutional or other affiliations. The complete name and address of the person who will handle reprint requests also should appear on this page.

Abstract

The abstract (approximately 150 words) should be a short summary, saying in brief what is said at length in the body of the article—rather than such and such "is discussed," "is presented," or "was investigated."

Tables and Figures

Tables

Each table should be typed on a separate sheet of paper, be numbered consecutively in Arabic numerals, have a brief descriptive title, and have its position indicated in the text.

Illustrations (Figures)

Three sets of clear, unmounted black and white glossy prints of figures should be submitted (preferably 5 by 7 inches, but no larger than 8½ by 11 inches). For line drawings, original artwork or glossy prints are acceptable. Illustrations should be numbered consecutively in Arabic numerals and the position indicated in the text. Figure number, first author's name and top of the photo should be shown on the reverse side of each illustration. Recognizable photographs of patients are to be masked and written permission for publication obtained from the patients.

Legends

All legends for figures should be typed together on a separate sheet of paper. Magnification and stain for photomicrographs should be indicated in parentheses.

Permission for Reproduction

If an illustration or table has been used previously in another publication, written permission for its use must be obtained from the publisher and should accompany the manuscript. The source should be acknowledged in the legend if it can be done briefly by citation of a reference number. Otherwise, acknowledgment is made at the end of the figure legend or at the bottom of the table.

References

References should be limited to those cited in the text and should be to medical, scientific, or scholarly publications. (Mass circulation periodicals are referenced in parentheses in the text.) They must be typed double-spaced and numbered consecutively as they appear in the manuscript.* (See examples below for style.) Abbreviations of journal titles should conform to those used in *Index Medicus*.

Journal Articles

Note handling of multiple authorship. If more than three authors are listed as contributors, use "et al" to designate those names after the first three. Also note capitalization, punctuation, use of inclusive page numbers, and year of publication. Separate the subtitle from the title by either a dash or a colon. Use colon *only* if it appears in the original citation.

1. Jones JS, Anderson HW, Johnson DW, et al: The athletic heart revisited—Sudden death of a 28-year-old athlete. JAMA 1978; 292:444-456

2. Graybill JR, Alford RH, Smith RG, et al: Cell-mediated immunity in cryptococcosis: A brief review. Cell Immunol 1978; 7:76-79

Books

Note handling of "edition," "editor(s)," and "volume," as well as appropriate sequence of reference information and capitalization of chapters and titles.

3. Berne EJ, Smith TL: Role playing in therapy, chap 2, Principles of Group Therapy. New York, Oxford University Press, 1966, pp 35-51 *(author of chapter same as author of book)*

4. Munsung JM: The role of drugs, chap 2, *In* Brest AN, Mayer JH (Eds): Hypertension—Vol 2, Therapy, 2nd Ed. Springfield, Ill, Charles C Thomas, 1961, pp 456-479 *(author of chapter different from authors of book)*

Pamphlets, Monographs, or Books With No Given Author

5. AMA Department of Drugs: AMA Drug Evaluation, 3rd Ed. Littleton, Mass, Publishing Sciences Group, 1977 *(corporate author)*

6. Compilation of Standard Definitions, 3rd Ed. Philadelphia, American Society for Testing and Materials, 1976 *(no given author; give name and place of publisher)*

Articles in Press or Accepted for Publication

Any article accepted for publication should include the name of the journal (appropriately abbreviated) in which it will appear and the phrase "in press" or "accepted for publication" in place of the date of publication.

Personal Communications and Unpublished Data

This information should *not* be included in the reference list but should be given in parentheses in the body of the text. Date of communication, whether it was oral or written, and the person's name, highest academic degree, and professional affiliation should be provided.

**Exception:* Articles for Topics in Primary Care and Epitomes use a limited number of authoritative references, both to the specific topic and the subject as a whole, that are *not* cited in the text and are listed in alphabetic order.

Acknowledgments

It is the policy of the *WJM* not to print acknowledgments, the feeling being that if a person has contributed enough to a paper to be mentioned, he or she should be included among the authors, or the contribution should be mentioned in the body of the paper or in a footnote.

Correspondence

Brief manuscripts commenting on articles that have appeared in the journal, containing information of interest to physicians, or discussing issues of the day will be considered for publication. Very short reports of cases, clinical experience, clinical studies, adverse effects, and the like also will be considered. Items for the Correspondence section should not exceed 600 words and should have no more than five bibliographic references and one figure or table.

Author Responsibility

Authors are responsible for all statements made in articles. Manuscripts are considered for publication with the explicit understanding that they are original, have not been published previously, and are not simultaneously under consideration by any other publication.

All accepted manuscripts are subject to copy editing, and authors are sent edited galleys for approval. No changes will be made after the final, edited version has been approved by the author.

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If reprints are desired, they must be paid for by the author. A reprint order form with schedule of prices is sent to the author when the article is published. Authors are responsible for handling requests for reprints of their articles.

Revised 10/1/87

WHEN ACID REFLUX ERUPTS

Zantac dramatically lessens pain of acid reflux[1] by inhibiting the formation of acid at its source–an action unique among pharmaceutical agents indicated for the treatment of gastroesophageal reflux disease.

Zantac® *Tablets*

ranitidine HCl/Glaxo *150 mg tablets bid*

The only H_2-antagonist indicated for the treatment of gastroesophageal reflux disease

1. Sontag S, Robinson M, McCallum R, et al: Ranitidine therapy for gastroesophageal reflux disease: Results of a large double-blind trial. *Arch Intern Med* 1987; 147:1485–1491.

See next page for Brief Summary of Product Information.

Glaxo/ ROCHE

ZANTAC® 150 Tablets
(ranitidine hydrochloride)
ZANTAC® 300 Tablets
(ranitidine hydrochloride)

BRIEF SUMMARY

The following is a brief summary only. Before prescribing, see complete prescribing information in ZANTAC® product labeling.

INDICATIONS AND USAGE: ZANTAC® is indicated in:
1. Short-term treatment of **active duodenal ulcer.** Most patients heal within four weeks.
2. **Maintenance therapy** for duodenal ulcer patients at reduced dosage after healing of acute ulcers.
3. The treatment of **pathological hypersecretory conditions** (eg, Zollinger-Ellison syndrome and systemic mastocytosis).
4. Short-term treatment of **active, benign gastric ulcer.** Most patients heal within six weeks and the usefulness of further treatment has not been demonstrated.
5. Treatment of **gastroesophageal reflux disease (GERD).** Symptomatic relief commonly occurs within one or two weeks after starting therapy. Therapy for longer than six weeks has not been studied.

In active duodenal ulcer, active, benign gastric ulcer, hypersecretory states, and GERD, concomitant antacids should be given as needed for relief of pain.

CONTRAINDICATIONS: ZANTAC® is contraindicated for patients known to have hypersensitivity to the drug.

PRECAUTIONS: General: 1. Symptomatic response to ZANTAC® therapy does not preclude the presence of gastric malignancy.
2. Since ZANTAC is excreted primarily by the kidney, dosage should be adjusted in patients with impaired renal function (see **DOSAGE AND ADMINISTRATION**). Caution should be observed in patients with hepatic dysfunction since ZANTAC is metabolized in the liver.

Laboratory Tests: False-positive tests for urine protein with Multistix® may occur during ZANTAC therapy, and therefore testing with sulfosalicylic acid is recommended.

Drug Interactions: Although ZANTAC has been reported to bind weakly to cytochrome P-450 in vitro, recommended doses of the drug do not inhibit the action of the cytochrome P-450-linked oxygenase enzymes in the liver. However, there have been isolated reports of drug interactions which suggest that ZANTAC may affect the bioavailability of certain drugs by some mechanism as yet unidentified (eg, a pH-dependent effect on absorption or a change in volume of distribution).

Carcinogenesis, Mutagenesis, Impairment of Fertility: There was no indication of tumorigenic or carcinogenic effects in lifespan studies in mice and rats at doses up to 2,000 mg/kg/day.

Ranitidine was not mutagenic in standard bacterial tests (*Salmonella, E. coli*) for mutagenicity at concentrations up to the maximum recommended for these assays.

In a dominant lethal assay, a single oral dose of 1,000 mg/kg to male rats was without effect on the outcome of two matings per week for the next nine weeks.

Pregnancy: ***Teratogenic Effects: Pregnancy Category B:*** Reproduction studies have been performed in rats and rabbits at doses up to 160 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to ZANTAC. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers: ZANTAC is secreted in human milk. Caution should be exercised when ZANTAC is administered to a nursing mother.

Pediatric Use: Safety and effectiveness in children have not been established.

Use in Elderly Patients: Ulcer healing rates in elderly patients (65 to 82 years of age) were no different from those in younger age groups. The incidence rates for adverse events and laboratory abnormalities were also not different from those seen in other age groups.

ADVERSE REACTIONS: The following have been reported as events in clinical trials or in the routine management of patients treated with oral ZANTAC®. The relationship to ZANTAC therapy has been unclear in many cases. Headache, sometimes severe, seems to be related to ZANTAC administration.

Central Nervous System: Rarely, malaise, dizziness, somnolence, insomnia, and vertigo. Rare cases of reversible mental confusion, agitation, depression, and hallucinations have been reported, predominantly in severely ill elderly patients. Rare cases of reversible blurred vision suggestive of a change in accommodation have been reported.

Cardiovascular: Rare reports of tachycardia, bradycardia, and premature ventricular beats.

Gastrointestinal: Constipation, diarrhea, nausea/vomiting, and abdominal discomfort/pain.

Hepatic: In normal volunteers, SGPT values were increased to at least twice the pretreatment levels in 6 of 12 subjects receiving 100 mg qid IV for seven days, and in 4 of 24 subjects receiving 50 mg qid IV for five days. With oral administration there have been occasional reports of reversible hepatitis, hepatocellular or hepatocanalicular or mixed, with or without jaundice.

Musculoskeletal: Rare reports of arthralgias.

Hematologic: Reversible blood count changes (leukopenia, granulocytopenia, thrombocytopenia) have occurred in a few patients. Rare cases of agranulocytosis or of pancytopenia, sometimes with marrow hypoplasia, have been reported.

Endocrine: Controlled studies in animals and man have shown no stimulation of any pituitary hormone by ZANTAC (ranitidine hydrochloride) and no antiandrogenic activity, and cimetidine-induced gynecomastia and impotence in hypersecretory patients have resolved when ZANTAC has been substituted. However, occasional cases of gynecomastia, impotence, and loss of libido have been reported in male patients receiving ZANTAC, but the incidence did not differ from that in the general population.

Integumentary: Rash, including rare cases suggestive of mild erythema multiforme, and rarely, alopecia.

Other: Rare cases of hypersensitivity reactions (eg, bronchospasm, fever, rash, eosinophilia) and small increases in serum creatinine.

OVERDOSAGE: Information concerning possible overdosage and its treatment appears in the full prescribing information.

DOSAGE AND ADMINISTRATION: Active Duodenal Ulcer: The current recommended adult oral dosage is 150 mg twice daily. An alternate dosage of 300 mg once daily at bedtime can be used for patients in whom dosing convenience is important. The advantages of one treatment regimen compared to the other in a particular patient population have yet to be demonstrated.

Maintenance Therapy: The current recommended adult oral dosage is 150 mg at bedtime.

Pathological Hypersecretory Conditions (such as Zollinger-Ellison syndrome): The current recommended adult oral dosage is 150 mg twice a day. In some patients it may be necessary to administer ZANTAC® 150-mg doses more frequently. Doses should be adjusted to individual patient needs, and should continue as long as clinically indicated. Doses up to 6 g/day have been employed in patients with severe disease.

Benign Gastric Ulcer: The current recommended adult oral dosage is 150 mg twice a day.

GERD: The current recommended adult oral dosage is 150 mg twice a day.

Dosage Adjustment for Patients with Impaired Renal Function: On the basis of experience with a group of subjects with severely impaired renal function treated with ZANTAC, the recommended dosage in patients with a creatinine clearance less than 50 ml/min is 150 mg every 24 hours. Should the patient's condition require, the frequency of dosing may be increased to every 12 hours or even further with caution. Hemodialysis reduces the level of circulating ranitidine. Ideally, the dosage schedule should be adjusted so that the timing of a scheduled dose coincides with the end of hemodialysis.

HOW SUPPLIED: ZANTAC® 300 Tablets (ranitidine hydrochloride equivalent to 300 mg of ranitidine) are yellow, capsule-shaped tablets embossed with "ZANTAC 300" on one side and "Glaxo" on the other. They are available in bottles of 30 (NDC 0173-0393-40) and unit dose packs of 100 tablets (NDC 0173-0393-47).

ZANTAC® 150 Tablets (ranitidine hydrochloride equivalent to 150 mg of ranitidine) are white tablets embossed with "ZANTAC 150" on one side and "Glaxo" on the other. They are available in bottles of 60 tablets (NDC 0173-0344-42) and unit dose packs of 100 tablets (NDC 0173-0344-47).

Store between 15° and 30°C (59° and 86°F) in a dry place. Protect from light. Replace cap securely after each opening.

August 1987

Glaxo

Glaxo Inc.
Research Triangle Park, NC 27709

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BOOKS RECEIVED

(Continued from Page 26)

MEDICAL BIOGRAPHIES—THE AILMENTS OF THIRTY-THREE FAMOUS PERSONS—Philip Marshall Dale, MD. University of Oklahoma Press, 1005 Asp Ave, Norman, OK 73019, 1987. 262 pages, $10.95 (paperback).

MEDICAL ECONOMICS PROBLEM SOLVER 1: PRACTICE MANAGEMENT—Edited by Ellen H. Bleiler. Medical Economics Books, Oradell, NJ 07649. 148 pages, $14.95 (paperback).

MEDICAL STAFF MONITORING FUNCTIONS: BLOOD USAGE REVIEW—Edited by Robert Fromberg. Joint Commission on Accreditation of Hospitals, 875 North Michigan Ave, Chicago, IL 60611, 1987. 37 pages, $30 (paperback).

A MULTIMODALITY APPROACH TO BREAST IMAGING—Saar Porrath, MD, Director, Woman's Breast Center, Santa Monica, California. Aspen Publishers Inc, 1600 Research Blvd, Rockville, MD 20850, 1986. 324 pages, price not given.

NEUROLOGY—PROBLEMS IN PRIMARY CARE—James L. Bernat, MD, Associate Professor of Clinical Medicine (Neurology), Dartmouth Medical School, and Chief, Neurology Section, Veterans Administration Medical Center, White River Junction, Vermont, and Frederick M. Vincent, MD, Associate Professor of Medicine and Psychiatry and Chief, Neurology Section, Department of Medicine, Michigan State University College of Human Medicine, East Lansing. Medical Economics Books, Oradell, NJ 07649, 1987. 605 pages, $39.95 (paperback).

NEW SURGICAL AND MEDICAL APPROACHES IN INFECTIOUS DISEASES—Volume 6 in Contemporary Issues in Infectious Diseases—Edited by Richard K. Root, MD, Professor and Chairman, Department of Medicine, University of California, San Francisco, School of Medicine; Donald D. Trunkey, MD, Professor of Surgery and Chairman, Department of Surgery, Oregon Health Sciences University School of Medicine, Portland, and Merle A. Sande, MD, Professor and Vice Chairman, Department of Medicine, University of California, San Francisco, School of Medicine, and Chief, Medical Service, San Francisco General Hospital. Churchill Livinstone Inc, 1560 Broadway, New York, NY 10036, 1987. 284 pages, $54.

OBSTETRICS, GYNECOLOGY, AND INFANT MORTALITY—Volume 3 in A Profile of Health and Disease in America—Wrynn Smith, PhD. Facts On File Inc, 460 Park Ave South, New York, NY 10016, 1987. 140 pages, $35.00.

OPEN HEART SURGERY—THEORY AND PRACTICE—Volume 7 in Surgical Science Series—Edited by John C. Callaghan, MD, FRCS(C), FACA, Professor of Surgery and Director, Division of Cardiovascular and Thoracic Surgery, The University of Alberta Hospitals, and Joseph Wartak, MD, Research Cardiologist, The University of Alberta Hospitals, and Associate Professor, Department of Applied Sciences in Medicine, The University of Alberta, Edmonton, Alberta, Canada. Praeger Publishers, 521 Fifth Ave, New York, NY 10175, 1986. 174 pages, $42.95.

PHARMACOTHERAPY OF RENAL DISEASE AND HYPERTENSION—Volume 17 in Contemporary Issues in Nephrology—Edited by William M. Bennett, MD, Professor of Medicine and Pharmacology and Head, Division of Nephrology and Hypertension, and David A. McCarron, MD, Professor of Medicine and Director, Oregon Hypertension Program, Division of Nephrology and Hypertension, Oregon Health Sciences University School of Medicine, Portland. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1987. 400 pages, $75.

THE PHYSICIAN'S GUIDE TO PRACTICE LOCATION BY STATE—1987-1988—Volume 1 (Alabama to Kentucky)—O. Sam Ashouri, MD. Doctors Publishing, Inc, 4221 Baymeadows Rd, Suite 2, Jacksonville, FL 32217, 1987. 346 pages, $36.90 (soft cover).

THE PHYSICIAN'S GUIDE TO THE TAX REFORM ACT OF 1986—Donald L. DeMuth, CPA, MBA, and Daniel C. Miller, CPA, MBA. Medical Economics Books, Oradell, NJ 07649. 131 pages, $19.95 (paperback).

PRACTICAL COMPUTER APPLICATIONS IN RADIONUCLIDE IMAGING—Volume 3 in Contemporary Issues in Nuclear Medicine—Edited by Arvis G. Williams, Jr, MD, Diagnostic Radiologist, Department of Radiology, Watson Clinic, Lakeland, Florida, and Christopher G. Eckel, MD, Assistant Professor of Radiology, University of New Mexico School of Medicine, Albuquerque. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1987. 282 pages, $52.

PRENATAL ULTRASOUND—A COLOR ATLAS WITH ANATOMIC AND PATHOLOGIC CORRELATION—Beverly A. Spirt, MD, Professor of Radiology; Lawrence P. Gordon, MD, Assistant Professor of Pathology; and Michael Oliphant, MD, Clinical Professor of Radiology, State University of New York Health Science Center at Syracuse. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1987. 143 pages, $70.

PRIMARY CARE OF CANCER—RECOMMENDATIONS FOR SCREENING, DIAGNOSIS AND MANAGEMENT—Regional Cancer Resource Center of Northeast Ohio; Edward A. Mortimer, Jr, MD, Editor in Chief. Case Western Reserve University School of Medicine, Cleveland, OH 44106, 1987. 190 pages, $15 (paperback).

PRINCIPLES OF EXTRACORPOREAL SHOCK WAVE LITHOTRIPSY—Edited by Robert A. Riehle, Jr, MD, Assistant Professor of Surgery (Urology), Cornell University Medical College; Assistant Attending Surgeon, and Director, Lithotripsy Unit, The New York Hospital-Cornell Medical Center, New York, and Robert C. Newman, MD, Assistant Professor of Surgery and Chief, Clinical Stone Service, Division of Urology, University of Florida College of Medicine, Gainsville. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1987. 248 pages, $48.

PROTOCOLS FOR HIGH-RISK PREGNANCIES—Second Edition—Edited by John T. Queenan, MD, Professor and Chairman, Department of Obstetrics and Gynecology, Division of Maternal-Fetal Medicine, Georgetown University School of Medicine, Washington, DC, and John C. Hobbins, MD, Professor of Obstetrics and Diagnostic Imaging, Yale University School of Medicine, and Director of Obstetrics, Yale-New Haven Hospital, New Haven, Connecticut. Medical Economics Books, Box C-779, Pratt Station, Brooklyn, NY 11205, 1987. 427 pages, $29.95 (paperback).

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'DYAZIDE' AS WRITTEN.

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Before prescribing, see complete prescribing information in SK&F CO. literature or PDR. The following is a brief summary.

* **WARNING**
This drug is not indicated for initial therapy of edema or hypertension. Edema or hypertension requires therapy titrated to the individual. If this combination represents the dosage so determined, its use may be more convenient in patient management. Treatment of hypertension and edema is not static, but must be reevaluated as conditions in each patient warrant.

Contraindications: *Concomitant use with other potassium-sparing agents such as spironolactone or amiloride. Further use in anuria, progressive renal or hepatic dysfunction, hyperkalemia. Pre-existing elevated serum potassium. Hypersensitivity to either component or other sulfonamide-derived drugs.*
Warnings: Do not use potassium supplements, dietary or otherwise, unless hypokalemia develops or dietary intake of potassium is markedly impaired. *If supplementary potassium is needed, potassium tablets should not be used. Hyperkalemia can occur, and has been associated with cardiac irregularities. It is more likely in the severely ill, with urine volume less than one liter/day, the elderly and diabetics with suspected or confirmed renal insufficiency. Periodically, serum K^+ levels should be determined. If hyperkalemia develops, substitute a thiazide alone, restrict K^+ intake.* ***Associated widened QRS complex or arrhythmia requires prompt additional therapy.*** *Thiazides cross the placental barrier and appear in cord blood. Use in pregnancy requires weighing anticipated benefits against possible hazards, including fetal or neonatal jaundice, thrombocytopenia, other adverse reactions seen in adults. Thiazides appear and triamterene may appear in breast milk. If their use is essential, the patient should stop nursing. Adequate information on use in children is not available. Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma. Possible exacerbation or activation of systemic lupus erythematosus has been reported with thiazide diuretics.*
Precautions: *The bioavailability of the hydrochlorothiazide component of 'Dyazide' is about 50% of the bioavailability of the single entity. Theoretically, a patient transferred from the single entities of triamterene and hydrochlorothiazide may show an increase in blood pressure or fluid retention. Similarly, it is also possible that the lesser hydrochlorothiazide bioavailability could lead to increased serum potassium levels. However, extensive clinical experience with 'Dyazide' suggests that these conditions have not been commonly observed in clinical practice. Angiotensin-converting enzyme (ACE) inhibitors can elevate serum potassium; use with caution with 'Dyazide'. Do periodic serum electrolyte determinations (particularly important in patients vomiting excessively or receiving parenteral fluids, and during concurrent use with amphotericin B or corticosteroids or corticotropin[ACTH]). Periodic BUN and serum creatinine determinations should be made, especially in the elderly, diabetics or those with suspected or confirmed renal insufficiency. Cumulative effects of the drug may develop in patients with impaired renal function. Thiazides should be used with caution in patients with impaired hepatic function. They can precipitate coma in patients with severe liver disease. Observe regularly for possible blood dyscrasias, liver damage, other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving triamterene, and leukopenia, thrombocytopenia, agranulocytosis, and aplastic and hemolytic anemia have been reported with thiazides. Thiazides may cause manifestation of latent diabetes mellitus. The effects of oral anticoagulants may be decreased when used concurrently with hydrochlorothiazide; dosage adjustments may be necessary. Clinically insignificant reductions in arterial responsiveness to norepinephrine have been reported. Thiazides have also been shown to increase the paralyzing effect of nondepolarizing muscle relaxants such as tubocurarine. Triamterene is a weak folic acid antagonist. Do periodic blood studies in cirrhotics with splenomegaly. Antihypertensive effects may be enhanced in post-sympathectomy patients. Use cautiously in surgical patients. Triamterene has been found in renal stones in association with the other usual calculus components. Therefore, 'Dyazide' should be used with caution in patients with histories of stone formation. A few occurrences of acute renal failure have been reported in patients on 'Dyazide' when treated with indomethacin. Therefore, caution is advised in administering nonsteroidal anti-inflammatory agents with 'Dyazide'. The following may occur: transient elevated BUN or creatinine or both, hyperglycemia and glycosuria (diabetic insulin requirements may be altered), hyperuricemia and gout, digitalis intoxication (in hypokalemia), decreasing alkali reserve with possible metabolic acidosis. 'Dyazide' interferes with fluorescent measurement of quinidine. Hypokalemia is uncommon with 'Dyazide', but should it develop, corrective measures should be taken such as potassium supplementation or increased dietary intake of potassium-rich foods. Corrective measures should be instituted cautiously and serum potassium levels determined. Discontinue corrective measures and 'Dyazide' should laboratory values reveal elevated serum potassium. Chloride deficit may occur as well as dilutional hyponatremia. Concurrent use with chlorpropamide may increase the risk of severe hyponatremia. Serum PBI levels may decrease without signs of thyroid disturbance. Calcium excretion is decreased by thiazides. 'Dyazide' should be withdrawn before conducting tests for parathyroid function. Thiazides may add to or potentiate the action of other antihypertensive drugs. Diuretics reduce renal clearance of lithium and increase the risk of lithium toxicity.*
Adverse Reactions: *Muscle cramps, weakness, dizziness, headache, dry mouth; anaphylaxis, rash, urticaria, photosensitivity, purpura, other dermatological conditions; nausea and vomiting, diarrhea, constipation, other gastrointestinal disturbances; postural hypotension (may be aggravated by alcohol, barbiturates, or narcotics). Necrotizing vasculitis, paresthesias, icterus, pancreatitis, xanthopsia and respiratory distress including pneumonitis and pulmonary edema, transient blurred vision, sialadenitis, and vertigo have occurred with thiazides alone. Triamterene has been found in renal stones in association with other usual calculus components. Rare incidents of acute interstitial nephritis have been reported. Impotence has been reported in a few patients on 'Dyazide', although a causal relationship has not been established.*
Supplied: 'Dyazide' is supplied as a red and white capsule, in bottles of 1000 capsules; Single Unit Packages (unit-dose) of 100 (intended for institutional use only); in Patient-Pak™ unit-of-use bottles of 100.

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New Developments in the Pathogenesis of Smoke Inhalation-Induced Pulmonary Edema

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Smoke inhalation causes most of the deaths in fire-related injuries, with pulmonary edema as a major determinant in the outcome of smoke-inhalation injury. The pathophysiology of pulmonary edema is thought to be related to the products of incomplete combustion. Damage to the integrity of the alveolar epithelium is one of the determinants of the development of smoke-induced pulmonary edema. In recent studies using lung clearance of aerosolized pentetic acid (DTPA [diethylenetriaminepentaacetic acid]) labeled with technetium Tc 99m to assess the permeability of the alveolar epithelium, several factors were identified that may increase a person's susceptibility to smoke-induced acute lung injury. These are increased initial alveolar permeability and alterations in the number and activity of alveolar macrophages. Clinical measurement of ^{99m}TcDTPA clearance may provide a sensitive and convenient method for the early detection and serial assessment of smoke-induced alveolar epithelial permeability changes.

(Witten ML, Quan SF, Sobonya RE, et al: New developments in the pathogenesis of smoke inhalation-induced pulmonary edema. West J Med 1988 Jan; 148:33-36)

Each year in the United States about 2 million people suffer burns that require medical attention.[1] Of these, 130,000 need hospital treatment and more than 50% require intensive care. Although each year 8,000 to 12,000 persons die of fire-related injuries, most deaths are not due to cutaneous burns but are caused by inhaling the toxic products of combustion.[2] The illness resulting from smoke inhalation can be divided into two major processes: the systemic effects of toxic gases such as carbon monoxide that are absorbed from the respiratory tract and the direct local effects of the inhaled substances on the respiratory system.[3] In this review we will focus on the pathophysiology of parenchymal lung injury produced by smoke inhalation.

Inhalation injuries are usually produced by gaseous or particulate products of incomplete combustion and are rarely due to heat unless steam is inhaled.[4] The combination of burning material and an enclosed space is a major determinant that can cause smoke inhalational injury. Recent incidents such as the takeover of an Egyptian airliner in Malta, the Air Canada airliner fire, and the Las Vegas MGM Hotel fire show the catastrophic combination of fire and an enclosed space. Additionally, increasingly more homes and public buildings are being built and furnished with flammable synthetic materials that yield copious smoke and gases when burned.

Numerous toxic gases are generated from the combustion and thermal degradation of synthetic materials such as polyvinyl chloride and polyurethane. Polyvinyl chloride is commonly used in furnishings and building fixtures. It does not burn until it reaches 475°C; from a temperature of 225°C until it burns at 475°C, however, it loses 60% of its weight by thermal degradation.[3] More than 75 known toxic products are formed in the process, including hydrogen chloride, chlorine, and phosgene.[5] Polyurethane combustion can result in the formation of isocyanate and hydrogen cyanide.[6]

Combustion of natural materials such as wood, cotton, paper, and so forth can result in the generation of numerous organic acids, aldehydes, and other noxious gases, including oxides of sulfur and nitrogen. Aldehydes, especially acrolein, can cause irritation of exposed mucous membranes and pulmonary edema.[7] Irritant gases such as ammonia and sulfur dioxide combine with water present in the lungs to form strong acids and alkalis.[2] Smoke particulate matter can absorb toxic gases, such as nitrous oxide and sulfur dioxide, and transport them to alveolar areas where they cause further damage.[8] Mucosal edema, bronchorrhea, and sloughed mucosa caused by chemical injury increase airway resistance and cause obstruction of airways.[3] Inhaled smoke particulate matter can cause bronchoconstriction, possibly by stimulating irritant receptors in the airways.[9]

In addition to airway injury, there is damage to the gas-exchanging areas of the lung. Within seconds surfactant activity in the lung is diminished, resulting in congestion followed by atelectasis.[2] When lung injury occurs, clinical and physiologic evidence is apparent soon after smoke inhalation. In the absence of surface burns, well-documented cases of pulmonary disease following smoke inhalation with a latency to onset of greater than 24 hours have not been reported.[10,11]

The trachea and upper airways have good heat-exchange properties. Consequently, the efficient cooling of the upper air passages makes thermal injury below the vocal cords uncommon, occurring in less than 5% of patients admitted to hospitals with surface burns.[12,13]

Inhaling the toxic constituents of smoke may damage both alveolar epithelium and capillary endothelium and result in an

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ABBREVIATIONS USED IN TEXT

BAL = bronchoalveolar lavage
DTPA = United States Pharmacopeial Convention, Inc. code designation for pentetic acid
LT = leukotriene
PG = prostaglandin
PGI_2 = prostacyclin
TX = thromboxane

increased permeability of the alveolar-capillary barrier. Edema forms by filtration of fluid across a damaged and excessively permeable membrane even when pulmonary capillary hydrostatic pressure is normal.

The diagnosis of pulmonary edema resulting from smoke inhalation is made on the basis of respiratory distress, impairment of oxygenation, and roentgenographic evidence of pulmonary edema in the absence of pulmonary venous hypertension. A study of 239 patients admitted to a hospital burn unit found that of 76 patients in whom pulmonary edema developed, 75% (57) died.[14] Patients involved in a closed-space fire conducive to producing large amounts of smoke and those with burns covering 50% of their surface area seemed to be at the greatest risk for the development of pulmonary edema. Another clinical study showed that 35 of 56 patients with smoke-inhalation injury had radiographic findings of pulmonary edema, such as perivascular fuzziness and peribronchial cuffing. Furthermore, these radiographic signs of pulmonary edema appeared in the first 24 hours after the injury.[15]

Other clinical studies have shown that the development of pulmonary edema occurs without a concomitant increase in the pulmonary capillary wedge pressure.[16,17] Measuring the extravascular lung water volume in burn patients with and without inhalation injury showed that, on admission, patients with parenchymal inhalation injury had elevated extravascular lung water volumes (10.1 ± 3.4 ml per kg body weight), whereas patients without parenchymal injury had significantly lower lung water values (3.9 ± 1.5 ml per kg). The accumulation of extravascular lung water and ventilation-perfusion scan abnormalities in the group with parenchymal inhalation injury occurred within hours of smoke inhalation. The normal hydrostatic pressures in these patients suggest that there was an increase in the pulmonary capillary membrane permeability. These clinical observations have been confirmed in sheep where smoke generated from burning cotton cloth caused changes in microvascular permeability to protein.[18] The inhalation injury produced a substantial change in lung lymph flow concomitant with an elevation in the lymph to plasma oncotic pressure ratio. These clinical and experimental findings provide evidence that the formation of pulmonary edema may be caused by an increase in the permeability of the alveolar-capillary barrier. Increased permeability allows fluid to leave the capillary and traverse the endothelial and epithelial layers of the alveolar-capillary barrier, resulting in pulmonary edema.

There is considerable evidence that the epithelial layer of the alveolar-capillary barrier is less permeable to solute than is the endothelial layer. The relatively greater resistance of the alveolar epithelium to solute movement is an important factor in understanding the probable sequence of events in the formation of smoke-induced pulmonary edema. Fluid fills the loose alveolar interstitium before it ruptures the epithelial layer and floods the alveolar spaces (Figure 1). Consequently, the permeability of the alveolar epithelium may be the most critical determinant leading to the development of pulmonary edema.

Several investigators believe that the pulmonary clearance of pentetic acid (United States Pharmacopeial Convention, Inc, code designation DTPA [diethylenetriaminepentaacetic acid]) labeled with technetium Tc 99m (molecular weight, 492 daltons) reflects permeability of the epithelial layer of the alveolar-capillary barrier.[19,20] Long-term exposure to cigarette smoke and the smoke of wood and diesel fires increases the ^{99m}TcDTPA alveolar clearance in humans.[21,22] Intense, short-term exposure to large amounts of smoke in rabbits also can increase the alveolar clearance of ^{99m}TcDTPA.[23] The amount of smoke required to increase the epithelial uptake of ^{99m}TcDTPA varied (5 to 35 tidal volume breaths). A tidal volume smoke breath is equivalent to smoking two cigarettes in a normal manner.[24] Rabbits pretreated with ibuprofen (25 mg per kg per day given intramuscularly), a cyclooxygenase eicosanoid inhibitor, for seven days before smoke exposure will have rapid increases in the alveolar clearance of ^{99m}TcDTPA, severe injury to type I alveolar cell epithelium (Figure 2), pulmonary edema, and a mortality rate of 61%.[25,26] Blockade of the arachidonic acid cyclooxygenase pathway could cause shunting of arachidonic metabolites to the lipoxygenase pathway. The death rate in these studies is comparable to the human experience after severe smoke inha-

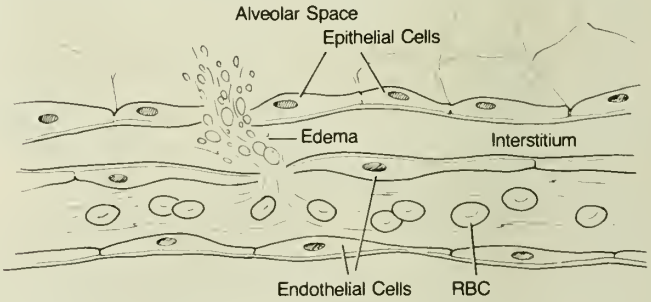

Figure 1.—A theory of the formation of smoke-induced pulmonary edema is that fluid fills the loose alveolar interstitial space before it ruptures the epithelial layer and floods the alveolar spaces. RBC = erythrocyte

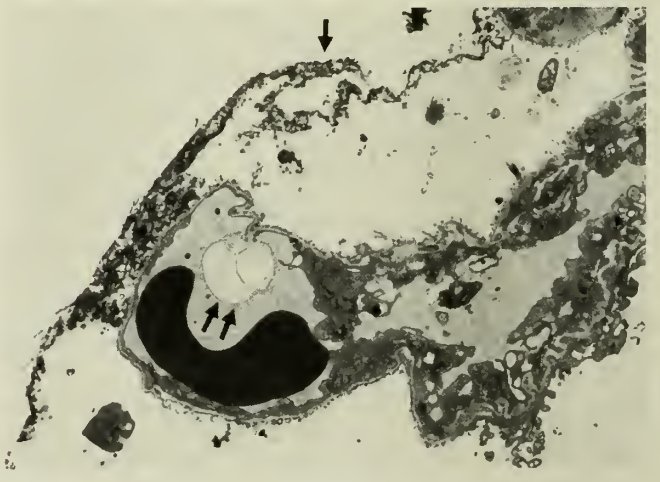

Figure 2.—The electron micrograph shows an alveolar septum in a rabbit treated with ibuprofen before smoke exposure. Smoke inhalation causes type I alveolar cell epithelium to form a membrane that is lifted off the alveolar wall **(single arrow).** A pale bleb of capillary endothelium is adjacent to an erythrocyte **(double arrows)** (uranyl acetate-lead citrate, original magnification × 9,540) (from Witten et al[25]).

lation. These experimental observations would tend to support the hypothesis that a critical determinant in edema formation after smoke inhalation is the integrity of the alveolar epithelium.

The particulate matter in smoke may be the constituent responsible for the development of increased alveolar epithelial permeability after smoke inhalation. Minty and Royston recently used a rat model to study the effects of cigarette smoke on alveolar epithelial permeability as measured by the clearance of ^{99m}TcDTPA.[20] Rats exposed twice a day to 90 puffs of cigarette smoke for seven days showed an increase in ^{99m}TcDTPA uptake. Filtered smoke did not cause increases in the ^{99m}TcDTPA uptake. These investigators suggested that particulates in cigarette smoke were responsible for the recruitment and activation of alveolar macrophages.

The contribution of inflammatory cells, such as alveolar macrophages, to the increase in alveolar permeability produced by smoke has been studied by bronchoalveolar lavage (BAL). In comparison to other smoke-exposed groups, ibuprofen-pretreated rabbits that died during smoke inhalation had a decreased number of alveolar macrophages and decreased leukotriene (LT) B_4 levels in addition to a more rapid rate of ^{99m}TcDTPA clearance.[26] In contrast, other studies have shown that alveolar macrophages are activated by smoke exposure. Long-term cigarette smokers can have a fivefold increase in alveolar macrophages compared with nonsmokers.[27] Rabbits with exposure to wood smoke had an increase in alveolar macrophages in both cell counts of BAL fluid and on electron micrographs.[28] Furthermore, smoke-exposed alveolar macrophages showed significant changes in surface features, possibly indicating activation. These studies suggest that changes in the alveolar macrophage number and activity are important in the development of the increase in alveolar permeability induced by smoke inhalation.

The mechanism by which changes in alveolar macrophage activity result in an increase in alveolar epithelial permeability after smoke inhalation is still not completely defined. It is possible, however, that chemical mediators released from inflammatory cells modulate the permeability of the alveolar epithelium.

Leukotriene B_4 is the major lipoxygenase metabolite of human alveolar macrophages.[29] Both in sheep lung lymph and alveolar fluid, a small increase in protein clearance occurred after LTB_4 (2 nmol per ml, 50 ml total) was administered in the alveoli of a caudal lung lobe through a fiber-optic bronchoscope. Staub and co-workers speculated that some of this effect may have been caused by a direct action of LTB_4.[30] When lung injury is induced by the administration of smoke, rabbits, including those pretreated with ibuprofen, had significant decreases in BAL LTB_4 concentration compared with controls. These data suggest that smoke exposure may have altered alveolar macrophage activity as evidenced by decreased LTB_4 production. Because, however, LTB_4 levels were reduced after smoke exposure, it is unlikely that LTB_4 was responsible for the increased lung permeability in the smoke-exposed rabbits. Other eicosanoids, such as thromboxane (TX) A_2, can modulate lung vascular permeability during complement and endotoxin injury processes.[31] Smoke inhalation, however, did not increase TXA_2 levels in BAL fluid or plasma.[26]

Chemical mediators released from lung parenchymal cells also might modulate alveolar epithelial permeability. It has recently been shown that levels of sheep lung lymph 6-keto prostaglandin (PG) $F_{1\alpha}$—a stable metabolite of prostacyclin (PGI_2)—increase after smoke exposure.[18] Prostacyclin is the major eicosanoid released by the endothelial cells of the alveolar-capillary barrier.[32(pp183,184)] In rabbits exposed only to smoke, 6-keto-$PGF_{1\alpha}$ levels are significantly increased in both BAL fluid and plasma. These rabbits had several focal areas of alveolar edema. Several investigators have postulated a protective role of prostacyclin in the lung,[33,34] but a recent observation fails to support this hypothesis. Rabbits pretreated with ibuprofen that survive smoke exposure have 6-keto-$PGF_{1\alpha}$ levels that are not increased and there is no pathologic evidence of lung injury.[26] Consequently, increased PGI_2 levels may be nothing more than a marker of endothelial cell injury. It is not known whether other eicosanoids may be released from lung parenchymal cells in response to smoke inhalation. Therefore, it appears that there is little evidence at this time to support a primary injurious or protective role for chemical mediators in the maintenance of alveolar epithelial permeability after smoke inhalation.

The initial permeability of the alveolar epithelial layer may play a role in the development of acute lung injury after smoke inhalation. Rabbits pretreated with ibuprofen that died during smoke inhalation had a significantly faster baseline alveolar clearance of ^{99m}TcDTPA than did ibuprofen-pretreated rabbits that survived smoke exposure.[25,26] Thus, it is possible that smoke particulate matter could have had greater access to lung parenchyma in these rabbits and could have caused acute lung injury. Humans also have shown a degree of variation in alveolar clearance of ^{99m}TcDTPA, and, consequently, there is a wide range of normal epithelial permeability. In the absence of a potentially injurious event such as smoke inhalation, there are probably no clinical consequences to a slight increase in the alveolar epithelial permeability. After smoke inhalation, however, an initial increased epithelial permeability could facilitate the development of pulmonary edema by increasing fluid flux across the alveolar-capillary barrier as well as allowing smoke particulate matter into lung parenchyma. There is a poor correlation clinically between the severity of smoke inhalational injury and the amount of pulmonary edema. Therefore, this observation may be explained by differences in susceptibility to smoke inhalational injury as determined by the permeability of the alveolar epithelium.

As suggested by recent experimental studies, measurement of alveolar epithelial permeability using ^{99m}TcDTPA offers a possible means of rapidly detecting smoke-induced injury to the alveolar-capillary barrier.[23,25,26] The use of ^{99m}TcDTPA in humans is becoming increasingly prevalent, although it is not yet a standard clinical procedure.[21,35-38] In addition, lung clearance of ^{99m}TcDTPA is sensitive to changes in alveolar permeability and is a relatively fast (less than 20 minutes) test to administer. Furthermore, serial periodic measurement of alveolar permeability with ^{99m}TcDTPA might be useful in following changes in a patient's condition with therapy. Therefore, in the future, the pulmonary clearance of ^{99m}TcDTPA may provide additional information to clinicians in the diagnosis and treatment of smoke-inhalation injury.

Lung scanning using xenon Xe 133 and bronchoscopy are other diagnostic methods used to determine the extent of smoke-induced lung injury. False-positive findings of xenon lung scans may occur, however, in patients with preexisting bronchitis, bronchiectasis, asthma, or pneumonia.[39] Unfortunately, no studies have yet been done comparing xenon lung

scans with ^{99m}TcDTPA lung clearance studies to determine the most effective method of detecting lung injury. Upper airway injury is diagnosed bronchoscopically when laryngeal or tracheobronchial erythema or edema and carbonaceous material or bronchorrhea are observed.[40] Therefore, bronchoscopy may provide information about upper airway injury that might be missed if only ^{99m}TcDTPA lung clearance studies were done. It is likely that ^{99m}TcDTPA lung clearance studies and bronchoscopy together give the most complete assessment of the extent of smoke inhalation injury.

In summary, research has identified several factors that may play crucial roles in determining the severity of lung injury and pulmonary edema after smoke inhalation. The permeability of the epithelial layer of the alveolar-capillary barrier and the number and activity of alveolar macrophages available as a defense against smoke particulate matter could determine the ultimate outcome for a smoke-inhalation victim. In addition, clinical measurement of the ^{99m}TcDTPA clearance may provide a sensitive and convenient method for detecting changes in alveolar epithelial permeability induced by smoke exposure.

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Rattlesnake Bites in Southern California and Rationale for Recommended Treatment

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Rattlesnake bite is most common in young men who often are intoxicated and have purposely handled a venomous snake. The incidence of bites is highest in the spring and early summer months, and they most often occur in the afternoon. The hands and feet only are involved in 95% of all bites. First-aid therapy should be limited to splinting the extremity and transporting the victim to a medical facility. Definitive therapy is administering antivenin (Crotalidae) polyvalent intravenously in adequate initial doses and repeating every two hours until the venom is completely neutralized. Serum sickness usually follows all doses of more than five vials but is readily controlled by giving corticosteroids. Bites are avoided by protecting the hands and feet, not handling venomous snakes, and using utmost caution while in the snakes' habitat.

(Wingert WA, Chan L: Rattlesnake bites in southern California and rationale for recommended treatment. West J Med 1988 Jan; 148:37-44)

In the United States, 8,000 people a year are estimated to be bitten by venomous snakes, an incidence of 3.74 bites per 100,000 population, with 14 to 20 deaths resulting.[1,2] This estimate was made more than two decades ago. With the rapid encroachment of humans into the natural habitat of rattlesnakes, particularly in the western deserts and mountains, it is likely that the incidence of snakebites has increased appreciably. The problem is compounded by the legal or illegal importing of venomous exotic snakes into the United States, some of which are sold in pet stores.[3]

In 1975 Russell and co-workers reported the experience of the Los Angeles County-University of Southern California Medical Center with 550 cases of snake venom poisoning.[4] In this report we review the cases of envenomation treated at the same center during the ensuing 11 years (January 1975 to January 1986), with recommendations for therapy based both on the experience of handling these cases and on recent developments in the field.

Patients and Methods

At this medical center, all patients with snakebite, regardless of age, are examined in the Communicable Disease Section of the Department of Pediatrics. The cases of 282 patients either seen as outpatients or admitted to the hospital were identified by a computer search of medical records. Most of these patients were seen in consultation with either Findlay E. Russell, MD, or one of us (W.A.W.). A protocol for treatment was available for the house staff if a consultant was not immediately accessible.

The following demographic variables were considered significant in assessing the degree of envenomation and the therapy required:

- Size and species of the offending reptile. Whereas rattlesnakes are venomous at birth and the venom of young snakes is more potent than that of older rattlesnakes,[5] mature snakes have a larger amount of venom stored in their venom glands. Hence, the bite of a large snake may be more dangerous. The lethality of venom varies widely among the various species of crotalids.[6(p139)] *Crotalus scutulatus*, the Mojave rattlesnake, possesses an extremely potent neurotoxic venom, indeed, one of the most lethal venoms among the world's reptiles. *Crotalus cerastes* (sidewinder), with the same distribution, has far less toxic venom. The venom of *Crotalus viridis helleri* (Pacific rattlesnake)—the only species native to the Los Angeles basin—is intermediate.
- Circumstances related to the bite: drug or alcohol abuse and accidental versus nonaccidental occurrence. A nonaccidental envenomation is defined as that occurring when a victim purposely handled the snake.
- The month and time of day the bite occurred. The optimal temperature range for maximal activity of rattlesnakes is 27°C to 32°C (80°F to 90°F),[7(p77)] which occurs during the day in the spring months and in the summer evening hours in southern California.
- The number of bites inflicted and the body area bitten.
- The first-aid methods used, because many such procedures are not done aseptically.
- The transport time required. In general, definitive therapy is more effective if administered as early as possible.
- Relationship of laboratory results to the envenomation. Venoms are complex compounds whose components vary with the species of snake. Venom affects every body organ and perhaps every cell. The major deleterious effects are directed toward the vascular system, the muscle and subcutaneous tissues, the blood, and the nervous system. The blood chemistry, urine analysis, and blood cell count and morphology reflect much of the damage.

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ABBREVIATIONS USED IN TEXT

Ig = immunoglobulin
LD_{50} = lethal dose for 50% survival of group

Assessment and Treatment

The severity of the envenomation was graded (see "Hospital Therapy") and related to the amount of antivenin required to neutralize its effects. The relationship of the skin test results and of the amount of antivenin administered to both serum sickness and side effects of the horse-serum antidote were compared.

Statistical Analysis

A total of 66 data elements were included in the study. One of us (W.A.W.) abstracted data from the medical records onto predesigned data forms, which information was later logged into a computer for analysis. The Statistical Analysis System was used for the statistical analysis.

TABLE 1.—*Characteristics of Rattlesnake Envenomation by Degree of Severity*

Characteristics	Grade of Envenomation: None	Minimal	Moderate	Severe	Total	P Value*
Patients, No.	3	61	138	25	227	...
Age, years						
Median (range)	26 (16-26)	21 (8-83)	22 (1-82)	23 (14-48)	22 (1-83)	...
Sex						
Male, No.	3	56	126	25	210 (93)†	...
Female, No.	0	5	12	0	17 (7)†	...
Month of incident						
January-March	0	6	15	5	26 (11)†	...
April-June	3	31	60	14	108 (48)†	...
July-September	0	13	38	6	57 (25)†	...
October-December	0	11	25	0	36 (16)†	...
Time of incident‡						
6 AM-10 AM	0	0	6	1	7 (3)†	...
10 AM- 2 PM	0	11	28	5	44 (20)†	...
2 PM- 6 PM	0	28	56	10	94 (43)†	...
6 PM-10 PM	3	13	32	6	54 (25)†	...
10 PM- 6 AM	0	7	5	3	18 (9)†	...
Related factors of incident						
Accidental, %	0	33	48	44	43‡	...
Alcoholic, %	33	25	26	44	28‡	...
Area of bite§						
Finger	2	48	95	11	156 (70)†	...
Hand	0	4	22	9	35 (15)†	...
Arm	1	0	3	0	4 (2)†	...
Torso	0	2	0	0	2 (1)†	...
Leg or foot	0	6	16	5	27 (12)†	...
Snake species, when determined						
Crotalus viridis helleri	1	47	119	22	189 (87)†	...
Crotalus scutulatus	2	1	5	2	10 (5)†	...
Crotalus cerastes	0	6	1	0	7 (3)†	...
Crotalus atrox	0	3	3	0	6 (3)†	...
Foreign	0	1	3	1	5 (2)†	...
Estimated size of snakes, cm						
Median	...	30	35	75	35	.05
Range	...	20-270	20-150	30-180	20-270	...
Number of bites						
One, No.	0	54	109	21	184 (81)†	...
Two, No.	2	6	27	4	39 (17)†	...
Three or more, No.	1	1	2	0	4 (2)†	...
First aid applied†‖						
Tourniquet	1	26 (29)	54 (61)	8 (9)	89 (39)	...
Incision	0	22 (28)	49 (62)	8 (10)	79 (35)	...
Suction	0	32 (32)	59 (58)	10 (10)	101 (44)	...
Splint	0	0	4	0	4 (2)	...
Cryotherapy	0	3	5	2	10 (4)	...
Hours from bite to treatment						
Median (range)	3 (1½-3½)	1 (1-27)	1 (½-12)	1 (1-24)	1 (½-27)	...

*Significant at $P = .05$ by the median test for medians or the Kruskal-Wallis test for means or the Mantel-Haenszel test for proportions: Comparison of differences of variable among the four grades of severity.
†The numbers in parentheses represent percentages.
‡These figures represent the median percentages of "Accidental" and "Alcoholic" causes of envenomations.
§Data are not available for some patients.
‖Some patients had more than one type of first-aid treatment applied.

(Continued on next page)

The data were analyzed to determine the differences of the severity of envenomation with respect to demographic and environmental factors, characteristics of bites, symptoms, treatment modality, laboratory findings, and the course and outcome of therapy. For each factor that was recorded as a categoric variable, the Mantel-Haenszel χ^2 test was used to test the significance of its association with the four severity groups. For each factor recorded as a continuous variable, the Kruskal-Wallis test was used. The nonparametric test was used because of the sample sizes in two of the four severity groups.

The Mantel-Haenszel χ^2 test was also used to determine the statistical significance of the relationship of the skin test results and of the amount of antivenin administered to both the occurrence of serum sickness and side effects of the horse-serum antidote.

Results

A total of 282 patients had a diagnosis of snakebite during the ten-year period, but 55 records were not available. Laboratory data were not complete in many of the 227 records reviewed, as many envenomations were mild and did not warrant extensive laboratory study. The histories were not always reliable because of the intoxicated state of a patient or a lack of careful observation of the circumstances by excited or by very young patients.

Demographic Characteristics of Bites

Our findings are summarized in Table 1, which also lists variables relating to the severity of envenomation. Male victims outnumbered females 9:1. Two thirds of the bites occurred during the months of April, May, June, and July. In all, 43% of the bites occurred in the afternoon (2 to 6 PM) and the next most frequent time periods were 10 AM to 2 PM (20%) and 6 to 10 PM (25%). Only 44% of the injuries were accidental; 57% of the victims had been handling a venomous snake, and 28% of the patients appeared intoxicated. The patients ranged in age from 1 to 83 years, the median age being 22 years and the average age 24. Of all the bites, 55% were in the age group of 17 to 27 years. Most of the injuries involved the fingers and hands (85%). Of the remaining bites, 13% were on the lower extremity, rarely above the ankle, and only 2% were elsewhere.

C viridis helleri accounted for 87% of the injuries, *C scutulatus* for 5%, *C cerastes* for 3%, *Crotalus atrox* for 3%, and other species for 2%. Bites by reptiles other than *C viridis helleri* occurred in patients referred from the Mojave Desert region or in persons who kept venomous or exotic snakes as pets. The size of the snake usually could be judged only by a patient's observation and therefore can be considered only an estimate. The size of the offending snakes varied from 20 to 270 cm. Most of the injuries were restricted to a single bite as manifested by one or two fang marks. Four patients had two or more bites, sustained when persistently handling the reptile even after the initial bite.

Treatment of the Bites

First-aid treatment was given to two thirds of the victims. In 35%, the bite area had been incised, rarely by equipment from commercial snakebite kits, but usually by any handy sharp instrument. Several patients bit their wounds. Suction was administered to 45%, usually orally. Suction sometimes was applied to the fang marks without incision. A tourniquet was applied to 40% of the bites and outmoded cryotherapy

(Continued from previous page)

TABLE 1.—*Characteristics of Rattlesnake Envenomation by Degree of Severity*

	Grade of Envenomation					
Characteristics	*None*	*Minimal*	*Moderate*	*Severe*	*Total*	*P Value**
Laboratory Tests						
Leukocyte count (median)/μl	8,500	8,800	9,050	10,700	9,100	...
Immature leukocytes (mean)/μl	..	3.3	4.1	5.8	4.1	...
Hemoglobin (mean), grams/dl	15.6	15.0	14.8	15.1	14.9	...
Hematocrit (mean), %	44.5	43.9	42.8	44.6	43.3	...
Creatine kinase (median), units/liter	91	202	192	312	205	.05
Fibrinogen level, % abnormal	0	38	29	57	35	...
Platelet count, % abnormal	0	0	4	8	3	...
Urinalysis						
Proteinemia, % patients	...	4	7	60	9	.05
Hematuria, % patients	...	0	8	50	9	.05
Patients with systemic reactions, %						
Paresthesia	0	55	80	92	73	.05
Ecchymosis	0	32	26	28	27	.05
Fasciculation	0	2	20	60	20	.05
Bullae	0	2	6	16	6	.05
Antivenin treatment						
Initial dose in vials						
Median (range)	...	5 (1- 7)	5 (1-17)	10 (2-25)	5 (1-17)	.05
Total dose in vials						
Median (range)	...	5 (1-12)	10 (1-26)	22 (10-43)	10 (1-43)	.05
Recovery time in days						
Median (range)	1 (1)	1 (0- 8)	1 (0- 8)	2 (1-13)	1 (1-13)	.05
Patients with tissue loss, %	0	5	4	4	4	...

*Significant at $P = .05$ by the median test for medians or the Kruskal-Wallis test for means or the Mantel-Haenszel test for proportions: Comparison of differences of variable among the four grades of severity.

was used in 4%, sometimes by an attending physician. Only 2% received splinting. Patients arrived promptly at medical facilities, the median time being one hour, but most obtained assistance within 30 minutes after the accident. The longest delay was 27 hours. Three victims were bitten without any reaction, a "dry bite." Reactions in 61 cases were considered mild, in 138 cases moderate, and in 25 severe. Demographic characteristics and the nature of the incident were not found to differ among the groups. The estimated size of the snake, however, and the physiologic reaction to the bite were positively correlated with increased severity: paresthesia, fasciculation, and the formation of bullae increased significantly with severity ($P = .05$).

The results of laboratory tests were of only minor assistance in assessing the severity of envenomation. The creatine kinase levels were significantly increased in patients with severe envenomation ($P = .05$), and the prothrombin times, fibrinogen levels, and platelet counts were altered substantially. No other laboratory test results showed notable abnormalities. Urine analyses, although infrequently done, tended to show proteinuria and hematuria more often in severe cases. Overt hemorrhage did not occur in any rattlesnake-envenomated patients. One patient, bitten by the rear-fanged imported *Rhabdophis subminatus*, experienced a severe coagulopathy requiring transfusion of 16 units of packed red cells over seven days.[3]

Of 227 patients, 211 received antivenin (Crotalidae) polyvalent and 16 were observed and treated symptomatically. Of those treated with antivenin, 82 (39%) received secondary doses. The initial antivenin doses, often administered in a referring medical facility, varied from 1 to 17 vials, with a median of 5 vials. The secondary doses, usually administered at our facility, ranged from 1 to 35 vials, with a median of 5 vials. The total dose ranged from 1 to 43 vials, with a median of 10. The total amount of antivenin, however, was related to the severity of the poisoning: patients with mild cases received a total median dose of 5 vials, moderately envenomated patients, 10 vials, and patients with severe envenomations, 22 vials. Recovery time also lengthened with increased severity.

Serum sickness was correlated positively with the total dose of antivenin. The median dose for the group with no serum sickness was 5.5 vials, the median for mild sickness was 10 vials, and for the most severe group, 15. No patient had severe serum sickness requiring either admission to hospital or prolonged treatment.

The skin test was an unreliable predictor of immediate systemic reactions (Table 2). Of eight patients with positive skin tests, urticaria and pruritus developed in only four, one of whom had a systemic reaction consisting of hypotension and bradycardia. Of 199 patients with negative tests, urticaria developed in 26 (13%), itching developed in 16 (8%), and edema developed in 5 (3%). Thus, a false-positive reaction occurred in 50% and a false-negative in about 8% of all tests. The intradermal skin test result also did not predict serum sickness.

Of the 94 patients who were observed in follow-up, serum sickness developed in 10. Of these, only two had a positive skin test before treatment. Of the 84 who were asymptomatic, 55 had negative skin tests ($P = .004$), actually a reverse result.

Several differences were noted between bites occurring in the daytime (10 AM to 6 PM) and those occurring at night. A significantly higher proportion of alcohol-related cases occurred at night (36% night, 23% day, $P = .04$). The night cases had a significantly higher proportion of injuries from species other than *C viridis helleri* (24% versus 6% $P = .008$), and the estimated size of the snake was found to be larger among the night injuries, an average of 60 cm versus 46 cm in the day cases.

TABLE 2.—*Relationship of Skin Test Reaction and Allergic Reaction to Antivenin*

Reactions	Negative Skin Test Group (N=199), %	Positive Skin Test Group (N=8), %	P Value*
Urticaria	13	50	.017
Itching	8	50	.004
Hypotension	6	13	.385
Bradycardia	1	13	.076
Apnea	1	0	.961

*By Fisher's exact test.

Therapy was limited to the use of antivenin. No fasciotomies were done, although the severely envenomated patients had massive edema of the bitten extremities. This edema invariably subsided without sequelae in five to ten days. Blebs, present in ten cases, were debrided on the fourth hospital day. Antibiotics were administered to 44 patients who either had severe envenomation or had received vigorous first aid.

The outcome of therapy was favorable. One death occurred in an 80-year-old man who suffered a myocardial infarction within 30 minutes of arriving at our center and before therapy was started. No amputations were done, and tissue loss was superficial except in a single case in which a child lost about 50% of the soft tissue from the distal phalanx of a severely bitten index finger. This required a reconstructive operation. Of those patients who required admission to hospital, half were discharged the following day, and 80% were dismissed within 48 hours. Only 10% remained more than three days, and these were seriously envenomated patients.

Discussion and Recommendations for Treatment

To understand the rationale of treatment for rattlesnake envenomation, a knowledge of the pharmacologic action of snake venom is helpful. *Crotalus* venom is a complex poison consisting chemically of 90% water, 5 to 15 enzymes, 3 to 12 nonenzymatic proteins and peptides, and at least 6 as-yet-unidentified substances. Basically, crotalid venom consists of two major pharmacologic components: The lethal factors responsible for the immediate death of prey are low-molecular-weight peptides and polypeptides consisting of 20 to 82 amino acid chains with molecular weights varying from 4,800 to 100,000.[8] These small proteins transiently damage the endothelial cells of vascular walls. On electron microscopy, there is blebbing of the endothelium, dilatation of the perinuclear spaces, and lysis of the plasma membrane.[9] The result is a microangiopathic vascular permeability to plasma, plasma proteins, and erythrocytes that "leak" into the surrounding tissues. This loss of fluid into the "third space" finally results in hemoconcentration, lactic acidosis, and hypovolemic shock. The same action on the pulmonary blood vessels results in pulmonary edema and hemorrhage, compounded by pooling of blood in the vasculature of the lung. This is a consistent autopsy finding.

The second function of venom relates to digestion.[6] Rat-

tlesnakes do not tear or shred food by mastication, but swallow their prey whole. Thus it is advantageous for the snake to introduce digestive enzymes into the bloodstream of an immobilized but still living prey, permitting distribution of the digestive enzymes throughout the tissues.[10] The enzymes important in changing human tissues include proteolytic enzymes or proteases that cause necrosis of muscle and subcutaneous tissues by a trypsinlike action[11]; L-amino acid oxidase catalyzes the oxidation of amino acids, causing tissue destruction; and phospholipase A_2, a general esterolytic enzyme, catalyzes the hydrolysis of the ester bond at the C2 position on lecithin, releasing a molecule of fatty acid and producing lysolecithin. Because erythrocyte membranes contain lecithin, the permeability of the cell wall may be altered, allowing water to enter the cell, and resulting in hemolysis and the precipitation of hemoglobin and ghosts of erythrocytes in renal tubules. Phospholipase A_2 also damages the plasma membrane of muscle cells, disrupts intracellular organelles, and causes an influx of calcium and an efflux of creatine and the muscle cell enzyme creatine kinase.[12,13] Necrosis of muscle fibers results. Serine esterase and other thrombinlike enzymes split fibrinogen molecules but remove only fibrinopeptide A from the molecule and do not activate factor XIII. An unstable fibrin clot results with the consumption of platelets and fibrinogen (disseminated intravascular coagulation). These clots are readily lysed by plasmin and by proteolytic enzymes in the venom. Afibrinogenemia, thrombocytopenia,[14] and profuse hemorrhage follow.

Current medical treatment generally is not based on that recommended for more than 2½ millenia. First aid for snakebite is an exception. Some time between 1000 BC and 600 BC, a Hindu physician, Sushruta, described and illustrated in the medical literature, the *Ayurveda,* the application of a tourniquet above the bitten area and incision and suction of the fang marks, followed by cauterizing the wound.[15] Only the cautery component of recommended treatment has failed to survive into the 20th century.

Early experiments in animals indicated that suction removed more than 50% of radioisotope-labeled venom injected subcutaneously into dogs, if the suction was instituted within three minutes.[16] These data have not been verified in humans, and not even a significant improvement in survival of experimentally envenomated animals has been shown with the use of this technique.[17] In our experience, incision and suction did not mitigate the severity of envenomation (Table 3), and they were frequently done by an excited nonphysician using an unsterile technique, resulting in a secondary infection that sometimes required plastic surgery or orthopedic repair. The use of constriction bands and tourniquets is based on impeding lymphatic return from a bitten extremity and presumably restricting venom to the wound site. The distribution of venom to body organs, however, certainly must occur through capillary, not lymphatic drainage, thus requiring the use of a tourniquet that completely occludes venous return. This would produce even more disastrous results than the bite itself. Because the swelling in the extremity appears to be plasma spreading through subcutaneous tissues, there would appear to be no benefit and even some disadvantage in restricting the edema to a limited area. Therefore, we recommend only the following measures, regardless of whether a patient has immediate access to medical care or is in a remote area where treatment will be delayed:

- Avoid excessive activity. Retreat out of the snake's accurate range, which is usually less than the length of the snake. Studies on experimental animals indicate that the median lethal dose (LD_{50}) of venom increases substantially by increasing the animal's activity.[18] Case studies, admittedly subjective, show a more severe hospital course in patients extremely active after envenomation compared with patients immobilized early.[19]

TABLE 3.—*Relation of First-Aid Treatment to Severity of Envenomation*

*Use of First Aid**	*None*	*Minimal*	*Moderate*	*Severe*	*Total*
Yes	1	40	90	16	147
No	2	20	47	9	78
Total	3	60	137	25	225
Patients receiving first-aid, %†		67	66	64	65

*First-aid treatment includes incision, suction, tourniquet, cryotherapy, or any combination thereof.
†χ^2 Test for association, $P=.7$, no relationship of severity to using first-aid

- Observe the approximate size of the snake. In our experience, larger snakes cause more severe envenomation.
- Immobilize the bitten extremity by splinting as if for a fracture.
- Mark the level of swelling with a pen, and write on the skin the time the mark was made. Repeat this procedure every 15 minutes during transport. The rapidity with which the swelling appears and progresses is an important factor in assessing severity.
- Transport the victim at a safe speed to the nearest medical facility that is equipped and staffed to care for envenomation—that is, one that has an adequate supply of antivenin available and a knowledgeable professional staff.

Hospital Therapy

Snakebites usually occur in young men in their third decade of life who have a blood alcohol concentration of more than 0.1%. Often they have been handling or attempting to feed a pet rattlesnake and have sustained a bite on the index finger. Although in other series a high incidence of bites is reported in children (50%),[20] only 19% of our patients were younger than 16 years.

The definitive therapy for rattlesnake envenomation is administering a specific antidote to the poison: antivenin in adequate amounts given intravenously and as early as possible. Secondary treatment consists of support of the various organ systems affected by the venom and avoiding modalities and drugs that are not effective and that may actually complicate the problem. Treatment in an emergency department may be carried out in the following ten steps, the sequence depending on the condition of the patient:

STEP 1. *Establish a physiologic baseline.* First, determine whether the patient was bitten by a poisonous snake. Signs of a bite of a venomous snake are fang marks, typically with ragged edges; local edema, usually limited to subcutaneous tissues because fangs usually penetrate only 1 to 8 mm[6]; ecchymoses around the bite site; variable pain; muscle fasciculations; paresthesias of scalp, face, and extremities; and a metallic taste in the mouth, especially in bites by the Pacific, diamondback *(C atrox),* and timber *(Crotalus horridus)* rattlesnakes.

The venom of *C scutulatus* may cause minimal local reac-

tion but produce neuromuscular blockade, shown early by cranial nerve palsies, and leading to respiratory paralysis.

Second, rapidly evaluate presenting signs and symptoms. Inquire specifically regarding the approximate time of the bite, first-aid methods, previous episodes of bites and the treatment used, known allergies, especially to horse serum and antibiotics, and the date of last tetanus immunization.

Next, take a blood specimen for a complete blood count and hematocrit determination. Request that the blood smear be examined carefully. Severe envenomation causes morphologic changes in erythrocytes, including spherocytosis and "burring" or pyknocytosis.[21] The hematocrit is a rough estimate of hemoconcentration.

The important coagulation studies are fibrinogen levels, fibrin-split products, and the platelet count. If the envenomation is severe, the following should be measured: blood urea nitrogen level, electrolytes, serum protein levels, blood gas tensions, and pH. These studies are not helpful in cases of moderate envenomation. An electrocardiogram is indicated for patients older than 50 years or those with a history of heart disease. A urinalysis should be done, with particular attention paid to the presence of protein and blood.

Measure and record (including time) the circumference of the injured extremity at the leading point of edema and 10 cm (4 in) proximal to this level. A mark on the skin with a felt pen is helpful in monitoring edema.

STEP 2. *Determine the severity of envenomation.* Severity depends on three factors: The size of the patient, the toxicity of the venom, which is species-related, and the quantity of venom injected—most rattlesnakes discharging between 25% and 75% of their venom in a single strike.[6,22] Therefore, knowing the size of the snake is important because the larger the snake, the greater the quantity of venom in their glands. Other important factors are the length of time the fangs remain embedded, allowing a greater discharge of venom; the number of bites sustained; interference by clothing, gloves, or boots; and the activity of the victim following the bite.

We use a grading system based on local and systemic reactions, the size and species of the snake involved, and the historical factors noted above. Reactions are graded as follows:

- No envenomation: Fang marks present but no local swelling or hemorrhage and no paresthesias (depending on species).
- Minimal envenomation: Fang marks, with local swelling limited to hand or foot and not progressing, and no systemic reactions.
- Moderate envenomation: Swelling progressing rapidly beyond the site of the bite, such as to the elbow or knee, systemic reactions, laboratory changes such as a fall in the platelet count or fibrinogen levels, a large offending snake, and more than one bite.
- Severe envenomation: Pronounced and rapidly progressive swelling, ecchymoses, severe generalized symptoms such as hypotension, and laboratory study abnormalities. A report of a large snake or a highly toxic species, such as *C atrox,* or multiple bites indicate a severe case of envenomation.

It should be emphasized that the grade of estimated severity when the patient is examined initially may *not* be the final picture. A mild case of envenomation that is inadequately treated may progress to a severe grade within hours.

STEP 3. *Do a skin test to determine sensitivity to horse serum.* For medicolegal purposes, follow precisely the instructions in the brochure enclosed in the package. Our study indicates that the skin test is not infallible and the results should be used only as a precautionary guide to further therapy. No systemic reactions to the skin test have occurred in more than 850 patients at this center.

STEP 4. *Start intravenous infusions in two extremities.* One line is for administering the antivenin. The second line is primarily for cardiovascular support, giving epinephrine and antihistamines or fluids, electrolytes, or colloid solution.

STEP 5. *Administer an adequate amount of antivenin (Crotalidae) polyvalent intravenously.* The following amounts diluted 1:4 with 0.5N saline solution should be administered for the first dose:

- No envenomation—no antivenin and no skin test.
- Minimal—5 vials (50 ml).
- Moderate—10 vials (100 ml).
- Severe—15 vials (150 ml).

Exceptions: Children and small persons (< 45 kg [100 lb]) should receive a *larger* dose by about 50%. Patients known to be bitten by *C scutulatus* should receive ten vials initially, then carefully monitored for delayed neurologic symptoms. To avoid allergic reactions, the infusion should be started at a very slow rate—such as 15 drops per minute—while observing the patient closely. If no reaction occurs in 15 minutes, the rate may be increased so that the solution is infused over two hours.

The initial dose of antivenin should be repeated every two hours until the progression of swelling has stopped and all paresthesias and muscle fasciculations cease. There is no maximal dose; the total dose is the amount required to neutralize the poison as measured by the clinical response.

Experiments in mice and rabbits have shown that venom labeled with iodine 131 can be detected in the circulation as long as 72 hours after injection (W.A. Wingert, MD, T.R. Pattabhiraman, PhD, and F.E. Russell, MD, unpublished data, January to June 1978). If this finding can be extrapolated to humans, antivenin should be of some value in symptomatic patients for at least 60 hours after envenomation.

Two types of anaphylactic reactions occur with horse serum: A type 1 allergic anaphylactic reaction caused by circulating immunoglobulin (Ig) E antihorse protein antibodies and an anaphylactoid reaction that may be due to direct degranulation of mast cells by the horse proteins with release of histamine or to activation of complement by either pathway with formation of the mediators prostaglandin G_2 and leukotriene. Either reaction usually is heralded by urticaria and pruritus and may be followed by severe laryngospasm and bronchospasm, hypotension, bradycardia, loss of consciousness, and possibly death. Anaphylactoid reactions may be avoided by premedicating patients with an antihistamine—that is, diphenhydramine hydrochloride, 50 mg (children, 1 mg per kg of body weight) given intravenously 15 minutes before giving the antivenin—then administering diluted antivenin at a slow rate initially. A positive skin test indicates the presence of IgE antibodies. The physician then must decide whether the patient will survive and not suffer substantial tissue loss without using antivenin. If the patient is seriously envenomated, however, antivenin may be successfully administered by diluting at 1:10, decreasing the rate of adminis-

tration, premedicating the patient with diphenhydramine, and titrating the patient's response by giving either epinephrine, 0.01 ml per kg, or more diphenhydramine intravenously.[23] A consultation through one of the Regional Poison Control Centers is suggested if this procedure is required.

Although the components of the venoms of each species of Crotalidae differ somewhat as indicated by the varying LD_{50}, they, fortunately, share enough components—phospholipase A_2 is common to all species—that the polyvalent antivenin neutralizes at least a portion of each species' venom. Unfortunately, the serum is processed by ammonium sulfate precipitation, which destroys as much as 50% of the neutralizing IgG, leaving most of the other proteins, α_1 and α_2 and β_1 and β_2, intact.[24] Physicians should not be deluded that this is a highly potent antidote, especially for bites of Crotalidae species, other than those species used in its production. An improved equine-derived antivenom is being developed by the procedure of polyacrylamide gel affinity chromatography, isolating the IgG fraction from the other proteins.[25] It is about five times as effective in neutralizing venom in human tissue culture and has not produced anaphylaxis in animals sensitive to horse serum. Further research has indicated that the Fab fragment of IgG (mole weight to 50,000) is as effective as the whole molecule (mole weight 150,000), is distributed more rapidly and more widely in body tissues, and is cleared renally in only nine hours.[26] These antivenoms must undergo extensive human trials before release by the Food and Drug Administration, however, and may not be available before 1989.

STEP 6. *Prevent secondary infection by administering an appropriate broad-spectrum antibiotic,* especially if unsterile first-aid measures were used. Pathogenic bacteria, predominantly gram-negative, occur in the snake's mouth (but not in the venom).[27]

STEP 7. *Prevent tetanus.* Tetanus rarely occurs following rattlesnake bite,[6] and snakes' mouths do not harbor *Clostridium tetani.*[27] It is prudent, however, to treat fang puncture wounds by adequately immunizing a patient, using a tetanus toxoid booster or hyperimmune tetanus globulin as indicated.

STEP 8. *Monitor and support the circulatory, respiratory, and hematologic systems.* Schaeffer and associates have repeatedly shown that crystalloid solutions do not correct shock in envenomated animals, and colloidal solutions are required.[28,29] Therefore, shock in humans should be treated with a plasma expander rather than a saline solution. Vasopressor drugs should not be used unless the intravascular volume has been restored.

We do not monitor for increased compartment pressure and have not encountered any adverse effects, even in massively swollen arms and legs. The edema fluid is reabsorbed in seven to ten days without sequelae. We do not recommend a fasciotomy. In a series of well-controlled experiments, Garfin and colleagues have shown that muscle necrosis is the direct result of proteolytic venom enzymes rather than intracompartmental pressure per se and that a fasciotomy done *before* injecting venom into a muscle did not alter the degree of necrosis resulting.[30]

Blebs and bullae forming in the edematous area should be debrided surgically between the third and fifth day after the danger of extensive bleeding is past. The area then is treated as a second-degree burn.

STEP 9. *Prepare to treat serum sickness during the following 21 days.* Corticosteroids are the drug of choice for treating serum sickness and should be administered at the first signs, usually urticaria and itching. If urticaria is treated with an antihistamine, the disease usually progresses in severity and is prolonged until steroids are used. The patient should be spared this complication. The steroids should be administered until all signs and symptoms have subsided for 24 hours and then the dose tapered over 72 hours. Our drug of choice is prednisone, 10 mg given four times a day for adults, or 1 mg per kg per day in children.

STEP 10. *Report all illegally possessed reptiles to the police or to the appropriate Fish and Game Agency.* Possessing a dangerous venomous snake without a permit is illegal in most states. The patient has broken the law and the snake may bite another victim, placing the physician at risk medicolegally for not reporting the initial incident.

A helpful large wall chart for hospitals and emergency departments detailing snake identification and medical treatment is available from the Arizona Poison Information Center, the University of Arizona, 1501 North Campbell Avenue, Tucson, AZ 85724.

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Medical Practice Opinion

EDITOR'S NOTE: *From time to time medical practice questions from organizations with a legitimate interest in the information are referred to the Scientific Board by the Quality Care Review Commission of the California Medical Association. The opinions offered are based on training, experience and literature reviewed by specialists. These opinions are, however, informational only and should not be interpreted as directives, instructions or policy statements.*

Radial Keratotomy

QUESTION:

Is radial keratotomy considered acceptable medical treatment for correction of myopia?

OPINION:

In the opinion of the Scientific Advisory Panel on Ophthalmology, it appears that radial keratotomy does have value for selected patients in reducing both myopia and dependence on the use of spectacles or contact lenses to correct that condition. However, the techniques of the procedure and its appropriate indications and contraindications are still evolving. Further, although often successful, the procedure is not uniformly predictable, and, though small, there is some risk of permanent damage to the eye. Long-term results are unknown. The risks and complications should be detailed for all patients undergoing the procedure, particularly those whose motivation is purely cosmetic.

All patients should be advised that a significant minority of patients have expressed dissatisfaction with the results of the procedure. Until the questions of long-term safety and effectiveness have been answered, this advisory panel thinks that radial keratotomy should be used with caution and with fully informed consent.

Approved: January 1981
Revised: May 1987

This opinion has been prepared by the CMA Scientific Advisory Panel on Ophthalmology based on available information. It is only an advisory opinion and should not be construed as binding on any individual or as expressing an absolute standard of medical practice. Medical opinion may vary regarding the appropriateness of a particular treatment or service in a given situation. Differences in an individual case should be reviewed by physician medical advisors. Differences of opinion between a medical advisor and attending physician should be referred to the county medical society where the physician practices.

Intravenous Rattlesnake Envenomation

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Intravenous envenomation by North American rattlesnakes is an uncommon occurrence, but a true emergency. In three documented, successfully resuscitated cases, the mainstay of treatment was the immediate intravenous administration of antivenin.

(Davidson TM: Intravenous rattlesnake envenomation. West J Med 1988 Jan; 148:45-47)

The vast majority of North American rattlesnake bites involve envenomation into the dermis and subcutaneous tissues. From there the venom is slowly absorbed, producing local, regional, and systemic symptoms. The basic medical treatment involves neutralizing the venom with the intravenous administration of polyvalent antivenin.[1,2] Rarely will a fang pierce a superficial vein and an intravenous bolus of venom be injected. In such cases, severe systemic symptoms can occur within one or two minutes. Such envenomations may be responsible for one or more of the 10 to 12 fatalities that occur each year in the United States.[2,3] In this article I describe three cases of intravenous envenomation. As a reference, an additional case of a typical dermal or subcutaneous envenomation is presented.

Reports of Cases

Case 1

The patient, a 12-year-old boy, was playing in his backyard. He saw a snake under a rock, reached under the rock to retrieve it, heard a buzzing, and was bitten on his right hand between the thumb and the first finger. Within minutes his hand began to hurt and swell. He and his older brother fished out the snake and killed it. His mother immediately brought him to the emergency department at Children's Hospital and Health Center in San Diego, where he was noted to have continued pain and swelling involving the entire dorsum of the right hand. Two fang marks were noted in the web of the hand. An infusion of lactated Ringer's solution was begun, and blood specimens were drawn for the following laboratory tests: a complete blood count, electrolytes, calcium, prothrombin time, partial thromboplastin time (PTT), platelet count, fibrinogen, creatinine, and blood urea nitrogen (BUN).

The child was tested intradermally for sensitivity to horse serum. After 20 minutes there was no reaction. The swelling had progressed above the wrist, and he reported tingling about his mouth. His respiratory rate increased slightly, he was diaphoretic, and fasciculations were present on the dorsal surface of his tongue. Lactated Ringer's solution was given at 100 ml per hour. Ten vials of antivenin were mixed in 100 ml of a saline solution and were given intravenously (IV) piggyback at 10 ml (one vial) every five minutes. After about five minutes, the child became restless and was noted to have an increased pulse rate. This was felt to be a reaction to the antivenin. The antivenin rate was slowed to one vial every ten minutes, the pulse reverted to normal, and the restlessness abated. The IV infusion rate was then increased, so as to deliver one vial every seven minutes. The patient tolerated this well. After three vials of antivenin, the local pain stopped and the swelling about the wrist stabilized. The first ten vials were given in an hour and 15 minutes, and the patient appeared stable. Fifteen minutes after stopping the antivenin therapy, the child's tongue again began to fasciculate, and he noted a return of the pain in his hand. Another five vials of antivenin were mixed in 50 ml of a warm saline solution and infused at a rate of one vial every seven minutes. The symptoms immediately ceased, but again recurred when the antivenin therapy was stopped. Another 5 vials of antivenin were administered intravenously, bringing the total to 20 vials. This time there was no recurrence of local or systemic manifestations. The child did report some circumoral tingling, and this persisted for 48 hours. He was otherwise well throughout the hospital stay. His laboratory values were normal except for the potassium level, which was slightly decreased. The data were normal midway through and following his treatment. The potassium value was normal the following day. His tetanus immunization was current. The patient was discharged from the hospital on the second postbite day, at which time most of the swelling had abated and he felt well.

The patient returned to the physician's office three days following the bite with a rash and hives about his trunk and abdomen. These were treated with diphenhydramine hydrochloride (Benadryl) and disappeared over the ensuing three days. The child made an uneventful recovery.

The purpose of this case presentation is to show the concept of titrating or neutralizing rattlesnake venom with antivenin and to demonstrate certain useful treatment principles.

Case 2

The patient, a 6-year-old girl, was bitten on her left ankle by an unidentified snake while alighting from her parents' car near Poway, California. She immediately screamed, fell to the ground, and became stiff with a clenched mouth and swollen lips and tongue. Her breathing became rapid. She was rushed to Pomerado Hospital in Poway, arriving there within 20 minutes of the bite. At that time the mother was trying to pry open the child's mouth.

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Reprints are not available.

ABBREVIATIONS USED IN TEXT

BUN = blood urea nitrogen
CVP = central venous pressure
ECG = electrocardiogram
IV = intravenous
P_{CO_2} = partial carbon dioxide pressure (tension)
P_{O_2} = partial oxygen pressure (tension)
PTT = partial thromboplastin time

The patient was hyperventilating and had respirations of 50 and a pulse rate of about 190 per minute. She was semicomatose, her face was massively swollen, and she had generalized fasciculations over her entire body. Two small puncture marks were evident over the medial malleolus of her left leg. Her skin was mottled in appearance. Venous and arterial blood specimens were drawn. Blood gas determinations made while the patient was breathing room air showed a partial oxygen pressure (P_{O_2}) of 108 torr, a partial carbon dioxide pressure (P_{CO_2}) of 20 torr, and pH of 7.12. She had a prothrombin time of 25.0 seconds (normal 10.5 to 13.0), and a PTT of greater than 120 seconds (normal 19.1 to 27.3). The BUN level was 13 mg per dl and serum sodium was 138, potassium 3.6, chloride 111, and bicarbonate 4.0 mEq per liter. Her serum glucose level was 270 and creatinine 0.8 mg per dl. The blood was described as grossly lipemic. The fibrinogen value was 154 mg per dl (normal 170 to 410). The blood specimen would not clot. Her hematocrit was 55%, hemoglobin 16.4 grams per dl, and the leukocyte count 22,800 per μl, which included 23% segmented forms, 75% lymphocytes, 1% monocytes, and 1% eosinophils. Her platelet count was 26,000 per μl, and crenated erythrocytes were noted on the blood smear.

On admission, the systolic blood pressure was 90 to 95 mm of mercury. An electrocardiogram (ECG) was interpreted as showing sinus tachycardia with a heart rate of 190, a PR interval of 0.12 seconds, QRS of 0.6 seconds, and a normal axis. An IV infusion of lactated Ringer's solution was started. One gram of methylprednisolone sodium succinate (Solu-Medrol) was given by IV push, and oxygen was delivered by mask. Over the next 25 minutes, 23 vials of antivenin were given by IV push. Each vial was injected over 10 to 20 seconds. Because of the time involved in mixing and injecting the antivenin, they were given one vial at a time. During this 25-minute period, the patient's condition substantially improved. Her respirations slowed, and her state of consciousness improved to the point where she could answer questions. Her breathing became normal, and the generalized fasciculations stopped. Mottling of the skin decreased, and the swelling about the child's face decreased considerably. Her blood gas values returned to normal while she was receiving oxygen by mask, showing a pH of 7.43, a P_{CO_2} of 35 torr, a P_{O_2} of 202 torr, and a base excess of 1.

The child's condition stabilized in the emergency department, and she was transported to Children's Hospital. On arrival there, about an hour and a half after the bite, her temperature was 38°C (100.4°F), pulse 160, and her respirations 52 per minute. Her blood pressure was 135/65 mm of mercury. On examination of the skin, hematomas were noted in the right inguinal area and in both antecubital fossae, all due to venipunctures. There was an abrasion on her left chest and her left ankle was mildly swollen. Two puncture marks 1.2 cm apart were noted over the left medial malleolus. Her face and lips were mildly edematous, and her mouth was bloody. She had some fasciculations of the facial muscles. Her pupils were equal, round, and reactive to light. Red reflexes were present in both eyes. Her ears were normal, and her physical examination otherwise showed no abnormalities. The patient was treated with vigorous IV hydration and received three units of fresh frozen plasma and six units of platelet concentrate. Her respiratory status remained stable. Her blood pressure and central venous pressures (CVPs) were normal, but were monitored as the child was on vigorous hydration in an effort to preserve renal blood flow and minimize kidney damage. The CVP remained in a stable range between 4 and 8 mm of mercury. The CVP line was removed on the third hospital day. At the time of admission to Children's Hospital, the patient was awake, alert, and responsive. Initially she was unable to move her extremities, and fasciculations were evident about her face; both conditions resolved over the first two hospital days.

Her hematologic values returned to normal within the first 24 hours. The patient was treated with an additional 7 vials of antivenin, giving her a total of 30 vials. On admission to Children's Hospital her hematocrit had fallen to 34%, and on the following day it was 24%. Her hematocrit at discharge was 25%, and no transfusions were required. The serum aspartate aminotransferase (formerly SGOT) level was elevated to 446 units per ml, and her serum alanine aminotransferase (formerly SGPT) value was also elevated to 96 units per ml. Her urine, which became red-tinged 60 minutes after envenomation, cleared in the first 24 hours, and urine output remained excellent. She was discharged from the hospital three days later and made a rapid, uneventful recovery.

Case 3

The patient, a 28-year-old laborer, was bitten by a 1.1-m (3½-ft) female southern Pacific rattlesnake *(Crotalus viridis helleri)*. The bite was to the ulnar surface of his wrist. Friends made a small incision over each fang mark and brought him to the Pomerado Hospital Emergency Department, where he arrived about 15 to 20 minutes after the bite. Over the next ten minutes, the patient became stuporous and finally comatose. Concurrently, his blood pressure declined rapidly and within ten minutes was unmeasurable. Bleeding was present at the site of envenomation. There was gross blood in his urine, and he was bleeding from the mouth and gingiva. Initial laboratory studies showed a hematocrit of 58%, a PTT of greater than 120 seconds over a control of 28.5, and a prothrombin time of 21 seconds over a control of 11.5. The platelet count was 46,000 per μl, and the fibrinogen level was 123 mg per dl.

The patient's blood pressure recovered with the rapid administration of large volumes of Ringer's lactate solution and albumin. He was given one gram of methylprednisolone intravenously. As rapidly as they could be reconstituted, 20 vials of antivenin were administered within the first hour of his arrival in the emergency department. The patient was transferred to the intensive care unit. Because of the low platelet count, the bleeding from the incisions on the bitten arm, and the hematuria, he was given an infusion of ten platelet packs. Following the first 20 vials of antivenin, his sensorium improved slowly. Over the first one to two hours, his right hand and arm became swollen, and as he regained consciousness he complained of severe pain in and around the bite site. Over the next two to three hours, the patient was treated with an additional 20 vials of antivenin.

Following the administration of a total of 40 antivenin vials, the swelling in the right arm ceased its progression, the pain dissipated, the hematuria cleared, and his sensorium continued to improve. Throughout this period, the patient had diffuse muscular fasciculations on the arms, legs, and face. At one point after 36 vials of antivenin were infused, urticaria developed, which was treated with the administration of diphenhydramine, 25 mg IV, and a brief withdrawal of the antivenin infusion. Fifteen minutes later, the antivenin infusion was resumed, with no recurrence of urticaria. Over the next 12 hours, the patient recovered his normal mental state and had complete stabilization of blood pressure, pulse, and respirations. During part of the resuscitation, he had been severely diaphoretic, with an elevated temperature of 39°C (103°F). This, too, cleared. By 12 hours after the bite, his urine was clear and remained so throughout his hospital stay. The following day his platelet count was 13,000 per μl, and another ten platelet packs were infused. Over the next several days he made an uneventful recovery, and by the fifth postbite day he had a 75% reduction in the swelling and edema of the right arm and hand.

Case 4

The patient, an 80-year-old man, was bitten on the dorsum of the left foot by a 0.8-m (2½-ft) female southern Pacific rattlesnake *(C viridis helleri)* near Hemet, California. The patient was bitten twice. He killed the snake and then returned 0.8 km (½ mi) by car to his home. Within minutes of being bitten, he experienced nausea, vomiting, dizziness, and swelling of his face and lips. His wife called for paramedics, who arrived in 30 minutes, and Life Flight (with an attending physician) arrived 45 minutes after the bite. At this time, he was given two vials of antivenin and transported to the University of California, San Diego, Medical Center. The Life Flight physicians reported that the patient was hypotensive with a systolic pressure of around 90 mm of mercury. His appearance was dusky, he was vomiting, incontinent of feces, and had markedly swollen lips and tongue. He was given 0.5 mg of epinephrine and brought to the intensive care unit. Here he was supported with a normal saline solution, epinephrine, and finally a dopamine hydrochloride drip. He was given two additional vials of antivenin.

Laboratory values in specimens drawn four hours after the bite were normal with the following exceptions: The prothrombin time was 16.6 seconds over a control of 11.6. The PTT was 33.4 seconds over a control of 25.9. The fibrinogen level was decreased to 285 mg per dl. A urinalysis showed 21 to 50 erythrocytes per high-power field, with 0 to 2 leukocytes per high-power field. Granular casts were also present. The ECG was normal. Because of the throat and tongue swelling, an endotracheal tube was inserted. Seven additional vials of antivenin were given at a slow infusion rate over the next several hours. Additionally, he was given 1 gram of methylprednisolone. Six hours after the bite, I saw the patient for the first time and suggested that he needed more antivenin. Additional vials were then injected, giving a total of 20. These were given IV piggyback at a rate of one vial per five to ten minutes.

On examination his foot was swollen, with significant ecchymoses developing on the ventral surface. A Penrose drain constricting band had been placed within the first hour of the bite and was still in place. This was released, and within the next five minutes his foot became exquisitely painful and rapidly increased 20% to 30% in circumference. By the time the first four to five additional vials of antivenin had been given, the pain in the foot dissipated, progression of swelling in his foot and ankle ceased, and his blood pressure returned toward normal. Within 45 minutes of beginning giving the additional antivenin, the dopamine drip had been stopped and there was a pronounced decrease in the patient's facial swelling, particularly of the lips.

During the next 12 hours, he had mild hematuria. Coagulation values quickly returned to normal, although his fibrinogen and platelet levels did not begin to return to normal until 36 to 48 hours after the bite. At about 36 hours, the patient insisted that the endotracheal tube be removed. The major problem in recovery was his low platelet count, which had bottomed out at 10,000 per μl and required several days to return to normal. When his coagulation values reverted to normal on the fifth day after the bite, he was discharged.

Discussion

In cases 1 to 3, the bites occurred in areas of prominent superficial veins. The diagnosis of intravascular envenomation was based on the extremely rapid onset of severe manifestations, a phenomenon that is rarely seen with North American rattlesnake dermal or subcutaneous envenomations. Because the venom was probably injected intravenously, it was active immediately, and hence neutralization with antivenin was required as quickly as possible. In cases 2 and 3, 20 vials of antivenin were given by IV push as rapidly as they were reconstituted. Because the rapid infusion of antivenin often elicits adverse physiologic responses, a gram of methylprednisolone (Solu-Medrol) was given to obviate these reactions. The efficacy and appropriateness of using steroids in cases of acute poisoning are indeterminate, but it was felt that they might protect against an acute immunologic response to the massive infusion of antivenin. Using steroids is not advocated for the usual dermal or subcutaneous envenomation.

With intravenous envenomation, it seems probable that one fang injects intravenously, while one fang delivers venom dermally or subcutaneously. In these cases, one must remember to treat the dermal or subcutaneous envenomation as well as the intravenous one. This requires additional antivenin, infused at a slower rate, and titrated against the local and regional signs and symptoms.

Case 4 was initially mistreated, and several points can be learned. First, the cardiovascular collapse was supported by administering fluids, epinephrine, and a dopamine drip. Second, the constricting band, in this case a Penrose drain, was left in place for about six hours. The foot was asymptomatic for this entire period. When the constricting Penrose was released, the patient experienced the rapid onset of pain and swelling, just as one sees in most rattlesnake envenomations by this species. While this is anecdotal, it strongly supports the use of a lymphatic retardant to keep the venom localized to the bite site until antivenin can be administered.

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Coffee and Pancreatic Cancer in a Rural California County

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In a study of the risk of fatal pancreatic cancer according to intake of regular and decaffeinated coffee, cases (N = 30) and controls (N = 47) were identified from death certificates and matched for age (± 5 years), sex, ethnicity, and date of death (± 5 years). Telephone interviews were completed with survivors of about 80% of both groups. In smokers, the relative risk for high (3 + cups) versus low (< 3 cups) intake of regular coffee was 4.3 (P < .05), and high versus low decaffeinated coffee, 5.5 (P < .05). In nonsmokers, neither type of coffee influenced the risk. Mean daily intakes of alcohol and cigarettes were virtually identical in cases and controls, although cases had accumulated nonsignificantly more pack-years. Intakes of regular and decaffeinated coffee were uncorrelated, and the smoking-coffee interaction could not be readily explained by recall bias. If coffee intake increases the risk of pancreatic cancer, the mechanism could depend heavily on smoking.

(Gorham ED, Garland CF, Garland FC, et al: Coffee and pancreatic cancer in a rural California county. West J Med 1988 Jan; 148:48-53)

Hsieh and co-workers recently reported an association between the intake of coffee and the risk of pancreatic cancer.[1] The report, an extension of the study by MacMahon and colleagues, suggested that the role of coffee was present but weak because it was absent until a relatively large amount (four cups per day) was consumed.[2]

The influence, if any, of coffee intake on the risk of pancreatic cancer continues to be a major concern. Cancer of the pancreas is the fourth leading cause of cancer death in the United States, and its incidence has tripled during the past three decades,[3] but incidence and mortality rates have leveled off since 1973.[4] Annual cases number 25,000 and deaths 24,000.[3] Studies other than those of MacMahon and Hsieh and associates[1,2] have reached mixed conclusions (Table 1), but in the study by Gold and co-workers, a statistically significant association was reported between the intake of coffee and the risk of pancreatic cancer in women, and a dose-response relationship was shown.[5]

Presented here is new evidence from a case-control study carried out in Imperial County, California, a rural county near San Diego.

Cases and Methods

All cases and controls were identified from death certificates on file at the Imperial County Department of Health Services. There were 51 deaths attributed to pancreatic cancer (International Classification of Diseases, Adapted, 9, code 157) in the county during 1978 to 1984. Decedents with death certificates mentioning pancreatic cancer in any position on the certificate were included; hospital records were not examined. Death certificates were selected unsystematically within each year until 30 cases whose survivors were willing to be interviewed were identified. Survivors of 38 cases were contacted; of these, 30 (79%) agreed to be interviewed. Survivors were traced from names listed on the death certificate, obituaries in back issues of the local newspaper, city directories, telephone books, and requests for survivors' addresses from the state department of motor vehicles. Controls were selected from death certificates and group-matched to cases by age (± five years), sex, ethnicity (non-Hispanic white, Hispanic, other), and year of death (± five years). One or more matched controls were identified and interviewed for each case. Any decedent without a malignant tumor was accepted as a control. Causes of death in controls were as expected at the ages pancreatic cancer occurs, including heart disease (47%), cerebrovascular disease (17%), pneumonia (4%), chronic obstructive pulmonary disease (4%), and miscellaneous causes (28%). Examination of approximately 3,800 consecutive death certificates during 1977-1981 yielded 94 that matched the cases for age, ethnicity, and year of death. Of these, 33 were deaths due to other cancers, suicide, homicide, or other violence and were excluded; 3 more were excluded because no informant was named on the certificate. Of the remaining 58 death certificates, interviews were obtained from survivors of 47 (81%). Response rates were similar in cases and controls; higher response rates were impossible to achieve owing to the advanced age of the decedents, many of whom were single or

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This research was supported in part by a grant from the Centers for Disease Control in Atlanta. Dr Cedric Garland was recipient of a Research Career Development Award from the US National Institute of Arthritis, Diabetes, Digestive, and Kidney Diseases, No. 1-K04-AM01083-04. The American Cancer Society, Imperial County Chapter, also supported this study.

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ABBREVIATIONS USED IN TEXT

SD = standard deviation
SEM = standard error of the mean

widowed without children to serve as informants on the death certificate. The terms "nonsmoker" and "smoker" refer to decedents who never smoked cigarettes compared with those who ever smoked cigarettes. The sole decedent who smoked a pipe but not cigarettes was considered a nonsmoker of cigarettes. Usual coffee intake ("How many cups of [insert type of coffee, regular or decaffeinated] did your [insert relationship] usually drink each day?") was queried separately for regular and decaffeinated coffee. Interviewing was done by volunteers affiliated with the American Cancer Society, Imperial County Chapter. Interviewers were unaware of the cause of

TABLE 1.—*Studies of the Association Between Coffee Intake and Risk of Pancreatic Cancer*

Study	*Design*	*Type of Controls*	*Matching Criteria*	*Results*
Lin and Kessler, 1981[6]	Case-control*	Hospital	Age, sex, race, marital status	Excess risk was noted in drinkers of decaffeinated coffee, but relative risk was not reported
MacMahon et al, 1981[2]	Case-control†	Hospital	Same hospital, same physician	Estimated relative risks in men for 0, 1-2, 3-4, and 5+ cups per day were 1.0, 2.6, 2.3, and 2.6, respectively; trend was not significant
				Estimated relative risks in women for 0, 1-2, 3-4, and 5+ cups per day were 1.0, 1.6, 3.3, and 3.1, respectively; *P* value for trend was <.001. After adjustment for age and sex and stratification for smoking, relative risks for 0, 1-2, and 3+ cups per day were 1.0, 2.1, and 3.1 for never-smokers; 1.3, 4.0, and 3.0 for ex-smokers; and 1.2, 2.2, and 4.6 for current smokers; *P* value for the trend with coffee intake after adjustment for age, sex, and smoking was .001
				After adjustment for age, sex, and smoking, estimated relative risks for 0, 1-2, and 3+ cups per day were 1.0, 1.8, and 2.7; the trend with coffee intake was highly significant
				Estimated relative risks in men for 0, 1-2, and 3+ cups of tea were 1.0, 0.7, and 0.8 (not significant)
				Estimated relative risks in women for 0, 1-2, and 3+ cups of tea were 1.0, 0.7, and 0.6 (not significant)
				Decaffeinated coffee was not analyzed separately
Jick and Dinan, 1981[7]	Case-control‡	Hospital	Age (±5 yr), sex, hospital or country, year admitted (±2 yr)	Compared with controls with *no cancer*, estimated relative risks for 0, 1-5, and 6+ cups per day were 1.0, 0.7, and 0.5, respectively, for both sexes combined
				Compared with controls with *other cancers*, estimated relative risks for 0, 1-5, and 6+ cups per day were 1.0, 0.6, and 0.8, respectively, for both sexes combined
				Decaffeinated coffee was not analyzed separately
Nomura et al, 1981[8]	Prospective			Age- and smoking-adjusted relative risks in Hawaiian men of Japanese ancestry for 0, 1-2, 3-4, and 5+ cups per day were 1.0, 1.5, 1.1, and 2.1, respectively; *P* value for trend = .085
				Decaffeinated coffee was not analyzed separately
Wynder et al, 1983[9]	Case-control§	Hospital	Age, race, sex, room status (ward, non-ward), and date of interview were used as strata in the analyses	After controlling for age, there was no association (estimated relative risk = 1.0) between coffee intake and pancreatic cancer in either sex; this was true with or without adjustment for cigarette smoking
				Decaffeinated coffee was not analyzed separately
Heuch et al, 1983[10]	Prospective‖			Relative risk for 7+ cups *v* ≤2 cups per day was .7
				Decaffeinated coffee was not analyzed separately
Whittemore et al, 1983[11]	Nested case-control¶		Age (same yr), sex (men only)	Relative risks for <2 and 2+ cups per day during college were 1.0 and 1.1. Association was not significant
				Decaffeinated coffee was not analyzed separately
				Relative risks for <2 and 2+ cups per day of tea during college were 1.0 and 0.5; this negative association was statistically significant at *P* = .05
Kinlen and McPherson, 1984[12]	Case-control#	Other cancers	Age (±5 yr), sex, area of residence	No association (estimated relative risk = 1.0) between intake of coffee and risk of pancreas cancer after adjustment for smoking and tea intake
				Decaffeinated coffee was not analyzed separately
				Estimated relative risks for intake of 0-2, 3-4, 5-9, and 10+ cups per day of tea were 1.0, 2.3, 2.3, and 2.6, respectively, after adjustment for smoking and coffee intake. The relative risks of 2.3 are both statistically significant at *P* < .05

*Controls were selected at random from among contemporaneous admissions to the same hospital. Only patients with pancreatic cancer were excluded. The study included 115 US hospitals during 1972-1975. There were 109 cases (67 men, 42 women) and 109 controls.

†Controls were all patients who were in the same hospital and under the care of the same physician at the time of the interview of the case. The study included 11 hospitals in metropolitan Boston and Rhode Island during 1974-1979. There were 369 cases (216 men, 151 women; age 0-79 yr) and 644 controls (307 men, 336 women).

‡Non-cancer controls were admitted for unspecified acute medical conditions or for surgical treatment of benign tumors. The cases were admitted to various hospitals in different countries. There were 83 cases, 83 non-cancer controls, and 78 cancer controls.

§The study included 17 US hospitals during 1977-1981. There were 275 cases (153 men and 122 women; median age 62 yr) and 7,994 controls.

‖The cohort size was 16,713 persons. It included a probability sample of Norwegian men (48%), Norwegian brothers of Norwegian-American men (20%), and siblings of both sexes of cases and controls from a previous unrelated study of gastrointestinal cancer (32%). Incidence was ascertained during 1964-1978 from the Cancer Registry of Norway using official birth numbers. There were 63 cases of pancreatic cancer in the cohort.

¶Cases were identified among 50,000 male former Harvard or University of Pennsylvania students who attended college during 1916-1950 and were followed for mortality through 1978. Four controls were chosen randomly for each case from students born in the same year and known to have survived the cases. There were 126 fatal pancreatic cancer cases (mean age 60.3 yr) and 504 controls.

#All controls had cancer, but those with the following cancers were excluded: lung, bladder, mouth, pharynx, esophagus, ovary. Coffee in this study was largely soluble (instant) or extract with chicory. Data on intake were collected in England and Wales during 1952-1954. There were 216 cases (109 men, 107 women; median age 74 yr) and 432 controls.

(Continued on next page)

death of the decedents. The median length of time between death and date of interview was six years for both cases and controls. Two cases were dropped from the analysis due to missing information on coffee intake, another because of an uncertain diagnosis, and one because a matched control could not be found.

The strength of association was analyzed using odds ratios to estimate relative risks, and statistical significance was tested using two-tailed χ^2 tests. When the expected value was less than five in any cell of a contingency table, Fisher's exact test was used.[15] Confidence intervals were calculated using a method described by Fleiss.[15] Adjustments and tests of significance of adjusted odds ratios were done using the Mantel-Haenszel technique and extension.[16,17] Dividing points approximating the overall mean intakes—that is, three cups per day of coffee and one cup per day of decaffeinated coffee—were used as cutoff points in the contingency tables.

Results

Mean age (± standard deviation [SD]) of the cases was 70.9 years (±11.3; standard error of the mean [SEM] 2.2 years); of controls, 73.6 years (±10.2; SEM 1.5 years). Cases were 46% male, controls 55% male. Cases were 85% non-Hispanic white, 12% Hispanic, 3% other; controls were 81% non-Hispanic white, 17% Hispanic, and 2% other. The interval between death and interview was similar (± two years) in cases and controls.

Of cases, 64% ever smoked compared with 59% of controls. Mean cigarette smoking (±SD) in cases was 38.16 pack-years (±43.5 pack-years) in controls, 28.72 pack-years (±37.5 pack-years). Median cigarette smoking in cases was 17.5 pack-years; in controls, 10.0 pack-years. Other smoking characteristics were similar in cases and controls (Table 2).

The patients with pancreatic cancer had a mean daily intake of beer of 9.5 oz (±27.7 oz; SEM 5.7 oz); wine, 0.2 oz

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TABLE 1.—*Studies of the Association Between Coffee Intake and Risk of Pancreatic Cancer*

Study	*Design*	*Type of Controls*	*Matching Criteria*	*Results*
Snowdon and Phillips, 1984[13]	Prospective**	...	...	Age- and sex-adjusted relative risks for <1, 1, and 2+ cups per wk were 1.0, 1.7, and 0.8, respectively. The association was not statistically significant Decaffeinated coffee was not analyzed separately
Gold et al, 1985[5]	Case-control††	Random-digit, hospital	Age (+5 yr), race, sex, date of admission	*Random-digit controls:* Age-adjusted estimated relative risks for 0, 1-2, 3-4, and 5+ cups per wk were 1.0, 1.5, 1.0, and 1.3, respectively, in men; and 1.0, 1.2, 1.6, and 2.9, respectively, in women; *P* value for linear trend was .05 in women, but not significant in men. After adjustment for age and sex and stratification by smoking, relative risks for 0, 1-2, and 3+ cups per day were 1.0, 1.4, and 1.2 for never-smokers; 0.7, 1.3, and 1.1 for ever-smokers; and 1.6, 1.5, and 3.2 for current smokers. None of the trends with coffee intake was statistically significant ($P>.05$) *Hospital controls:* Age-adjusted estimated relative risks for 0, 1-2, 3-4, and 5+ cups per wk were 1.0, 1.6, 1.5, and 1.0, respectively, in men; and 1.0, 0.8, 2.0, and 2.1, respectively, in women; *P* value for linear trend was 0.1 in women; not significant in men. After adjustment for age and sex and stratification by smoking, relative risks for 0, 1-2, and 3+ cups per day were 1.0, 1.3, and 1.3 for never-smokers; 0.7, 0.9, and 1.5 for former smokers; and 0.7, 1.6, and 2.0 for current smokers; none of the trends with coffee intake was statistically significant ($P>.05$) There was no statistically significant association between intake of tea (ever, never) and pancreatic cancer Decaffeinated coffee was not analyzed separately from coffee containing caffeine
Hsieh et al, 1986[1]	Case-control‡‡	Hospital	Same hospital, same physician	Compared with controls with *gastrointestinal* disorders, age- and sex-adjusted estimated relative risks for 0, 1-2, 3-4, and 5+ cups per day were 1.0, 1.2, 1.0, and 2.5, respectively, for both sexes combined; the trend was not statistically significant Compared with controls with *nongastrointestinal* disorders, age- and sex-adjusted estimated relative risks for 0, 1-2, 3-4, and 5+ cups per day were 1.0, 1.5, 1.2, and 2.6, respectively, for both sexes combined; while the trend was not significant, the relative risk of 2.6 was significantly different from 1.0 No increased risk was found for intake of decaffeinated coffee, alcohol, or tea
Mack et al, 1986[14]	Case-control§§	...	Matched on age, sex, race, and ethnicity	Estimated relative risks for both sexes of intakes of 0, 1-4, and 5+ cups per day were 1.0, 1.5, and 2.0; the trend was not statistically significant. After stratification by smoking, relative risks for men for intakes of 0, 1-4, and 5+ cups per day were 1.0, 1.5, and 2.9 in never or ex-smokers and 1.8, 3.3, and 3.1 in current smokers. Corresponding relative risks for women were 1.0, 1.5, and 1.0 in never or ex-smokers and 4.4, 3.9, and 4.9 in current smokers

**The cohort consisted of 23,912 male and female Seventh-Day Adventists followed during 1960-1980. All cases (N=71) were identified from the California death certificate file. It is believed that this study population drank a larger proportion of coffee in soluble (instant) or decaffeinated form than the general population.

††Random-digit controls were matched on telephone exchange, age (±5 yr), race, and sex. Hospital controls were selected from the same 16 Baltimore-area hospitals as the cases and matched on age (±5 yr), race, sex, and date of admission. Patients with any type of cancer were excluded from the controls. There were 201 cases (48% males and 52% females; mean age 66.1 yr), 274 random-digit controls, and 201 hospital controls.

‡‡Controls were selected as in an earlier report during 1974-1979.[2] Cases and controls came from the same hospitals as in the 1974-1979 study but were obtained during 1981-1984. There were 172 cases (85 men and 87 women; age 0-79 yr) and 267 controls (129 men and 138 women).

§§Cases were ascertained from a population-based cancer registry during 1976-1981. Controls were selected by canvasing residential units adjoining the cases' homes. There were 490 cases aged 0-64 years (282 male and 208 female) and 490 controls. Study period was 1976-1981.

(±0.7 oz; SEM 0.15 oz); and liquor, 0.8 oz (±1.6 oz; SEM 0.33 oz); a total daily ethanol intake of 0.49 oz (±0.91 oz; SEM 0.19 oz) (14.01 grams; ±25.70 grams; SEM 5.36 grams). Controls had a mean daily intake of beer of 10.3 oz (±25.9 oz; SEM 3.9 oz); wine, 0.3 oz (±0.9 oz; SEM 0.14 oz); and liquor, 0.8 oz (±2.0 oz; SEM 0.30 oz) total daily ethanol intake of 0.68 oz (±1.25 oz; SEM 0.187 oz); or 19.26 grams (±35.54 grams; SEM 5.30 grams).* The distribution of the daily total intake of ethanol was also similar in cases and controls (Table 3).

The mean daily intake (±SD) of regular coffee—that is, with caffeine—in cases was 4.71 cups (±3.5 cups; SEM 0.716) and in controls was 3.17 cups (±2.90 cups; 0.430). The distribution of the usual daily intake of regular coffee for cases and controls is shown in Table 4. The estimated relative risk for an intake of 3+ cups per day of coffee was 2.7 (Table 5).

Because smoking has been associated with pancreatic cancer, the population was subdivided according to cigarette-smoking habits. There was no association in nonsmokers but a statistically significant association in smokers. When an adjustment for smoking was made, the estimated relative risk dropped to 1.9 and was no longer statistically significant (Table 6). While the effect of coffee disappeared in nonsmokers (estimated relative risk = 1.1, not significant), the estimated relative risk in smokers rose to 4.3 ($P < .04$).

Overall, there was no correlation ($r < .005$, $P = .48$) between number of cups per day intake of decaffeinated and regular coffee (Table 7). Of the 67 decedents in the study for whom there was information on both regular and decaffeinated coffee intake, 50 drank exclusively regular coffee, 3 drank exclusively decaffeinated, 11 drank both, and 3 drank neither. For this reason, it was possible to analyze the effect of a usual intake of decaffeinated coffee on the risk of pancreatic cancer. The usual daily intake of decaffeinated coffee in cases and controls is shown in Table 8. There was an increased risk associated with the use of decaffeinated coffee that was independent of the use of regular coffee. The effect of decaffeinated coffee was almost as strong as that of regular coffee (Table 9).

Stratification by smoking (not shown) showed that the effect was confined to ever-smokers (odds ratio = 5.5, $\chi^2 = 3.92$, $P < .05$). There was no effect of decaffeinated coffee in those who never smoked (odds ratio = 1.0, $\chi^2 = 0.00$, $P = .99$).

Correlation analyses were done for the association between the daily intake of regular and decaffeinated coffee and packs per day of cigarette smoking. The association ($r = +.53$) between the intake of regular coffee and cigarette smoking was significant ($P < .00001$); between decaffein-

*Assumes that a typical container of beer contains 12 oz, which is customary for beer sold canned or bottled in this county; that a glass of wine contains 4 oz; and that a hard-liquor drink contains 1.5 oz of liquor; percent alcohol, weight for weight, was assumed to be 3.6% for beer, 12.6% for wine, and 36% for liquor.[15]

TABLE 2.—*Cigarette Smoking Characteristics by Case or Control Status, Imperial County, California, 1978-1984*

Packs/d, No.	Cases No.	Cases Percent*	Controls No.	Controls Percent*
None	9	35	20	43
0.1-0.4	2	8	5	11
0.5-1.4	5	19	12	26
1.5-1.9	3	12	2	4
2.0+	6	23	7	15
Unknown	1	4	1	2
Total	26	101	47	101

	Cases	Controls
Median packs/d	0.9	0.2
Mean (SD) packs/d	1.03 (1.00)	0.75 (0.88)
90% CI (2-tailed) packs/d	0.701-1.359	0.540-0.960

Smoking History	Cases Mean	Cases SD (SEM)	Controls Mean	Controls SD (SEM)
Duration of smoking (yr)†	21.3	19.8 (3.9)	20.0	21.0 (3.1)
Age started smoking (yr)‡	22.7	13.2 (3.3)	25.6	14.9 (3.1)
Pack-years	38.2	43.5 (8.9)	28.7	37.5 (5.6)

CI=confidence intervals, SD=standard deviation, SEM=standard error of the mean

*Totals add up to more than 100% due to rounding off of percentages.
†Based on all cases and controls.
‡Based on the 16 patients who smoked cigarettes and the 26 controls who smoked cigarettes.

TABLE 3.—*Mean Daily Intake of Ethanol by Case or Control Status, Imperial County, California, 1978-1984*

Grams Ethanol/d (oz)	Cases No.	Cases Percent*	Controls No.	Controls Percent*
0.00	10	38	15	32
0.01 (0.00 oz)-3.9 (0.13 oz)	5	19	11	23
4.0 (0.14 oz)-9.9 (0.35 oz)	3	12	3	6
10.0 (0.36 oz)-19.9 (0.7 oz)	1	4	7	15
20.0 (0.8 oz)-39.9 (1.4 oz)	2	8	6	13
40.0 (1.5 oz)-99.9 (3.5 oz)	2	8	3	6
100.0 (3.6 oz)+†	2	8	2	4
Unknown	1	4	0	0
Total	26	101	47	99

*Totals add up to more or less than 100% due to rounding off of percentages.
†Includes cases with intakes of 104.1 grams (3.7 oz) and 122.5 grams (4.3 oz) per day and controls with intakes of 138.2 grams (4.9 oz) and 175.0 grams (6.2 oz) per day

TABLE 4.—*Daily Intake of Regular Coffee by Case and Control Status, Imperial County, California, 1978-1984*

Daily Intake of Coffee, cups/d	Cases No.	Cases Percent	Controls No.	Controls Percent*
0	2	8	4	9
0.1-1.9	1	4	6	13
2.0-2.9	4	15	13	28
3.0-3.9	5	19	9	19
4.0-4.9	3	12	4	9
5.0-9.9	5	19	5	11
10.0+	4	15	3	6
Unknown	2	8	3	6
Total	26	100	47	101

*Total adds up to more than 100% due to rounding off of percentages.

TABLE 5.—*Pancreatic Cancer According to Intake of Regular Coffee, Imperial County, California, 1978-1984*

Daily Intake of Coffee, cups/d	Cases	Controls
3+	17	21
<3	7	23
Total*	24	44

Odds ratio (95% confidence interval)=2.7 (1.0-6.8)

*Information on intake of regular coffee was not available for 2 cases and 3 controls (not shown).

ated coffee intake and cigarette smoking, it was slight ($r = -.17$, $P = .09$). There was virtually no association between years of drinking regular and decaffeinated coffee ($r = -.05$, $P = .36$).

Discussion

This study is the first to show an effect of drinking coffee on the risk of pancreatic cancer that is almost completely limited to cigarette smokers. Lin and Kessler's early study[6] indicated that decaffeinated coffee use was one of several risk factors (such as occupation as a dry cleaner or working in a gasoline station) that could play a role in a multifactorial pattern of causation, but they did not report a risk from using regular coffee. MacMahon and colleagues reported that drinking regular coffee—that is, with the ordinary content of caffeine—was associated with pancreatic cancer, as we report here.[2]

Previous studies have been criticized for a lack of appropriate controls.[2,7] Most case-control studies have excluded controls with smoking-related illnesses (Table 1). This created a situation where controls were more representative of the nonsmoking population and cases were more representative of the smoking population. Because smoking cigarettes and drinking coffee tend to be done more often than expected by chance by the same people, the procedure would tend to increase the chances that cases would have smoked more and consumed more coffee than controls.

This study, that of Gold and co-workers,[5] and that of Lin and Kessler[6] avoided this possible bias by selecting possibly more representative control groups, an inherently more conservative procedure when testing for the effects of smoking cigarettes and drinking coffee (because coffee use is related to smoking, $r = +.53$, $P = .00001$). Despite this conservative approach, which would tend to underestimate the relative risk for coffee and smoking, the effect of coffee intake on the risk in smokers was strong, suggesting that the underlying relative risk may be considerably higher than reported here.

There are both advantages and disadvantages of matching on vital status.[18] When both the cases and controls have died, information is obtained from survivors of both and is directly comparable. Furthermore, personal habits such as smoking tend to be reported accurately by spouses or other close relatives. In a study of shipyard workers, there was 83% concordance between husbands and wives interviewed separately and simultaneously on the husbands' smoking habits.[19] In another study of 1,841 subjects in which they were interviewed about their smoking habits and later relatives were interviewed about the subjects' smoking habits after the subjects had died, there was 92% agreement between the subjects' and survivors' responses.[20] In both studies the results were analyzed for evidence of systematic recall bias, but none was found.[18]

The principal disadvantage of using controls matched on vital status—that is, the control decedents in this study—is similar to that found with hospital controls. The controls may not be adequately representative of the overall population of similar age and other characteristics.[18] The control group in this study consisted mainly of persons who died of cardiovascular and cerebrovascular diseases, for example, who may have smoked more than members of the general population of this community. The proportion of the control group who were smokers was 57%, whereas the proportion of the US population of similar age, sex, and race who smoked during about the same time period was 45%.[21] This suggests that the use of controls who were deceased made it more difficult to detect an effect of smoking than would have been possible in a prospective study or in a study with controls who were not matched as we did here on vital status. The effect of smoking on the risk of pancreatic cancer would not be detected with this study unless it was larger than the overall effect of

TABLE 6.—*Estimated Relative Risks of Pancreatic Cancer According to Intake of Regular Coffee and Cigarette Smoking History, Imperial County, California, 1978-1984*

Daily Intake of Coffee, cups/d	Smoking History* Never Cases	Never Controls	Ever Cases	Ever Controls
3+	4	9	12	12
<3	4	10	3	13
Total	8	19	15	25

Odds ratios (95% confidence intervals), never smoked=1 1 (0 0-5.8), ever smoked=4 3 (2.0-9 2); smoking-adjusted odds ratio=1 9, P=.18

*Information was unavailable on smoking history or daily intake of coffee for 3 cases and 3 controls.

TABLE 7.—*Joint Distribution of Usual Intake of Regular and Decaffeinated Coffee, Imperial County, California, 1978-1984**

Regular Coffee, cups/d	Decaffeinated Coffee, No. of Cups/d 0	1	2	3+	Total
0	3	2	1	0	6
1	6	0	0	0	6
2	14	2	1	0	17
3	11	2	0	1	14
4	5	1	1	0	7
5	3	1	0	0	4
6+	11	1	0	1	13
Total	53	9	3	2	67

*r<.005, P=.48.

TABLE 8.—*Daily Intake of Decaffeinated Coffee by Case and Control Status, Imperial County, California, 1978-1984*

Decaffeinated Coffee, cups/d	Cases No.	Cases Percent	Controls No.	Controls Percent
0	16	67	37	84
1	6	25	3	7
2	1	4	3	7
3+	1	4	1	2
Total*	24	100	44	100

*Excludes 2 cases and 3 controls for which there was no information on the use of decaffeinated coffee.

TABLE 9.—*Pancreatic Cancer According to Intake of Decaffeinated Coffee, Imperial County, California, 1978-1984*

Daily Intake of Decaffeinated Coffee, cups/d	Cases	Controls
1+	8	7
<1	16	37
Total*	24	44

Odds ratio (95% confidence interval)=2.6 (0.8-8.6).

*Excludes 2 cases and 3 controls for which there was no information on the use of decaffeinated coffee.

smoking on the various causes of death of the controls. Furthermore, the relatively small sample size available for study in this small rural community may have made it more difficult to detect an effect of smoking or other risk factors as compared with studies generally carried out in urban populations with a larger number of cases.

Relative risks may appear to be higher or lower than the actual value if there are other systematic differences in recall. Survivors almost never expressed uncertainty about a decedent's smoking or coffee-drinking habits of cases or controls in this family-oriented farming community. Differential recall depending on cause of death might nonetheless explain some of the associations. Better recall of the joint existence of the habits of drinking coffee and smoking cigarettes in survivors of cases as compared with those of controls could possibly explain the interaction present in this study. We know of no reason, however, to suspect that recall of the combination of these habits would be different in survivors of cases as compared with controls.

Another possible source of bias is that some controls may have quit drinking coffee owing to the diseases that caused their deaths, artifactually raising the odds ratios. Coffee drinking, while equivocally associated with peptic ulcer disease, is not proscribed in the diseases that caused death in most of the controls—that is, cardiovascular, cerebrovascular, and respiratory. It is nevertheless possible that the controls, either on their own initiative or in response to advice from physicians or others, cut down on their intake of coffee. This could possibly have artifactually raised the odds ratios reported here.

We used the usual intake as the measure of intake of coffee in this study. Pancreatic cancer has a rapidly fatal course, and nine out of ten patients die within a year of diagnosis.[22(p182)] A usual intake is more likely to indicate a lifetime exposure to coffee than recent intake because habits may change during the year between diagnosis and death and possibly during a period of unknown duration preceding the diagnosis. It was made clear during the interview that the usual intake in this study referred to the usual intake throughout an adult lifetime, and respondents rarely, if at all, expressed difficulty with this concept.

We believe the evidence on coffee drinking and pancreatic cancer warrants further consideration, particularly in smokers. Most previous studies have attempted to control for smoking as a confounder rather than regarding it as a necessary condition for coffee drinking to produce the disease.

The effect was similar in smokers whether regular or decaffeinated coffee was consumed, but caffeine may or may not be important in the chain of causation. Decaffeinated coffee intake may reflect an earlier or a current intake of coffee containing caffeine.

It is still premature to suggest a mechanism for the effect we have reported. The pancreas releases digestive enzymes every one to two hours to maintain "housekeeping" in the bowel as part of the interdigestive motor complex.[23] Either regular or decaffeinated coffee (or caffeine itself) causes an increase in interdigestive secretion by the pancreas of trypsin precursors.[24]

Cigarette smoking has the same effect. Smokers who were fasted overnight and withdrawn from cigarettes for 18 hours were shown to have longer periods of pancreatic secretion (phase II of the interdigestive period) between meals than were nonsmokers.[25] The periods returned to normal after resuming smoking; the period of prolonged secretion appears to persist four to five hours after the evening meal.[23]

We found no effect of alcohol use on the risk of pancreatic cancer, as reported in a review on this question.[26] The clear absence of an effect of alcohol use in this study may have made it easier to detect the effect of coffee intake.

The assertion by Hsieh and colleagues that there is no excess risk of pancreatic cancer associated with an intake of less than four cups per day of regular coffee[1] may be too optimistic in light of our findings, particularly for smokers. The combination of consuming coffee and smoking cigarettes is widespread in the United States, and the population attributable risk for the combination could be high.

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Medical Progress

Modern Techniques of Pain Management

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Even clinicians who keep up with the research literature on pain mechanisms may find themselves uncertain when trying to bring these new theories down to practical application for a patient with pain. The areas of dysfunction to be attacked should be systematically outlined, a complementary set of treatments be decided on, and follow-through be done in a reasonable number of visits. Physicians must also know when to refer a patient who goes beyond their own assessment and treatment skills.

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Pain as an initial or continuing complaint cuts across many medical and surgical disciplines and is probably a component of most problems seen in initial consultations. Working with their own skills, with outside consultants, or in a multidisciplinary setting, clinicians should be able to localize the sites of nociceptive activity within the nervous system, identifying their causes and perpetuating factors, and outline a series of treatments that could interrupt or modulate the perception of pain by patients.

Of great help in this endeavor is the increasing flow of basic science discovery into practical clinical application.[1] At the beginning of this decade, few citations could be found under the heading "pain" in the *Index Medicus*. In 1986 the number had multiplied, representing journals from family and general internal medicine, pediatrics, surgery, neurology, anesthesiology, dentistry, nursing, and various other clinical and research subspecialties. There are many publications devoted to the examination of pain alone, perhaps the only symptom to ever receive such intensive scrutiny. As clinicians overcome their protective resistance to getting "too involved" with their chronic pain patients, however, and reassess the key factors in their cases, they can appreciate that chronic, persistent pain is as much a disease as a symptom, with risk factors, a predictable course and prognosis, and many symptomatic treatments, with few available cures.[2] Clinicians should train their patients to look on their pain in the same way they would look on chronic pulmonary disease or circulatory problems, where modern management also goes beyond prescribing a few drugs and offering a return appointment.

Acute pain is "alerting" or "useful" pain, signifying tissue injury from a medically or operatively remediable somatic cause. It is often accompanied by signs of autonomic hyperactivity—diaphoresis, mydriasis, tachycardia, or changes in blood pressure. Anti-inflammatory, analgesic, and antianxiety drugs are commonly used as adjuncts to "tender, loving care" in progress to recovery, ideally with no permanent disability. Chronic pain, however, persists beyond what was felt to be curative treatment, losing its urgent significance. The typical pattern is about six months' application of serial monotherapies—chasing a "cure" but yielding only partial relief and numerous exacerbations. Patients become psychologically conditioned to their pain and illness behavior and may head down the road toward nonrecovery and permanent disability. Adjunctive remedies useful for acute pain are inappropriate in a case of chronic pain—that is, narcotic and tranquilizer tolerance and dependence quickly develop, and patients are at an increasing risk of analgesic end-organ damage and accelerating chronic pain behavior, reinforced by well-meaning, concerned friends, relatives, and physicians. In such a situation, it behooves a clinician to direct treatment toward the behavioral components and away from acute pain therapies (Table 1).

Often cases of chronic pain are artificially divided into benign or malignant pain categories, depending on whether the cause is noncancerous or cancerous, or related to local complications of cancer treatment. Certainly a patient with persistent pain from a life-threatening, mutilating, and incurable disease will have different psychosocial factors operant, but the somatic and behavioral approaches to the pain can and should be the same as those for a patient with chronic benign pain, with obvious additions: appropriate testing to rule out recurrent disease, a more frequent use of narcotic analgesics, and more aggressive nerve blocking or neurosurgical ablative techniques for a patient with cancer pain and a limited (less than six months) life expectancy.[3,4]

Transmission and Perception of Nociceptive Stimuli

Knowledge of the neurophysiologic concomitants of pain perception continues to grow and to directly affect the clinical management of pain complaints (Table 2).[5] Each component needs to be evaluated and treated.

Understanding of the peripheral mechanisms is critical in differentiating persistent acute pain states from those chronic pain states in which there are no clear abnormalities in peripheral structures. Often overlooked is the contribution to persistent acute pain of abnormal sympathetic discharges from the lateral horns of the thoracolumbar cord or their associated spinal ganglia and postganglionic segments.[6] Triggered by often minimal or unrecognized somatic causes, this neural

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activity is perceived as intensely painful, with cutaneous hypersensitivity, abnormal vasoregulation, and the risk of severe end-stage trophic changes, as in classic causalgia or reflex sympathetic dystrophy. It does not respond to treatments appropriate for somatic or visceral afferent-mediated pain and should be specifically looked for and treated in all patients with persistent pain (sympathetic nerve blockade).

In the central nervous system, nociceptive inputs traverse Rexed laminas I and V (perhaps also IV and VI), and second-order neurons ascend in the contralateral spinothalamic tract to the lateral, ventral, and caudal thalamus, from which third-order neurons communicate with areas of the sensorimotor and association cortices. Parallel impulses ascend through the spinoreticulothalamic tract from deeper or visceral structures to more medial thalamic structures and limbic areas. The limbic-cortical projections allow integration of incoming nociceptive signals with a patient's ongoing arousal or emotional state, prior pain experience, and other learned indicators to determine the patient's ultimate experience of "pain"—which may be quite different from the original stimulus intensity. Lesions (deafferentation) of dorsal roots or in these nociceptive pathways in spinal cord, midbrain, or thalamus may result in spontaneous, increased activity at the next most rostral segment and the development of severe, usually burning, "central pain."[7] Like sympathetic-mediated peripheral pain, central pain will not respond to the same treatments used for peripheral afferent-initiated pain. It should also be ruled out in all pain states (differential spinal or epidural nerve block will relieve peripheral neuropathic pain, but not centralized pain).

TABLE 1.—*Pain Models*

Acute Pain	*Chronic Pain*
Alerting and useful pain	Pain without urgent significance
Classical medical-operative cure	Prolonged duration with Serial monotherapies Numerous exacerbations Learned illness behavior
Adjuvant drugs and care Narcotics, other analgesics Steroids, nonsteroidal anti-inflammatory drugs Antianxiety drugs "Tender, loving care"	Inappropriate acute pain medication Narcotic, tranquilizer dependence Analgesic end-organ damage Reinforcement of illness behavior with "tender loving care"
Recovery, no permanent disability	Nonrecovery, permanent disability

TABLE 2.—*Components of the Pain Response**

	Nervous Response	
Nociception	*Peripheral*	*Central*
Transmission		
Anatomic	Free nerve endings Unmyelinated and myelinated afferents	Dorsal horn projection cells Excitatory interneurons Spinothalamic and spinoreticulothalamic tracts Ventroposterolateral and medial thalamus Cerebral cortex
Chemical	Arachidonic acid— leukotrienes, prostaglandins Bradykinin Histamine Polypeptides— substance P, somatostatin, vasoactive intestinal polypeptide, cholecystokinin	Neurotensin
Modulation		
Anatomic	Large myelinated afferents	Inhibitory interneurons Descending systems— corticoperiaqueductal medullary; medullospinal
Chemical	?	γ-Aminobutyric acid— ?glutamic acid, glycine Endorphins Serotonin—5-hydroxytryptamine Norepinephrine
Perception (cognitive-evaluative) Dependent on level of arousal, attention, and past pain experiences		
Suffering (affective-motivational) Dependent on mood, past emotional responses to pain, sociocultural expectations, and adequacy of environmental social support		
Pain Behavior Apparent responses to nociception, perception, and suffering Can be operantly conditioned to other environmental stimuli		

*Adapted from Wall and Melzack.[5]

Modulation of Nociceptive Stimuli

Incoming nociceptive signals are altered by segmental and suprasegmental mechanisms that can enhance or limit their transmission both spatially and temporally. The original gate-control theory is insufficient to explain all the observed phenomena.[8-10] But concurrent activity in non-nociceptor sensory pathways (the large-fiber/dorsal column system) clearly does alter nociceptive input at spinal-segmental, thalamic, and possibly cortical levels by both presynaptic and postsynaptic inhibition. Nociceptive activity itself in one dorsal root can inhibit transmission through adjacent roots, most likely by presynaptic inhibition through cells in laminas II and III (substantia gelatinosa). Inputs to lamina V may mediate the phenomena of the "inhibitory surround" for input from cutaneous regions. Interactions at these layers could also be responsible for the accommodations of small myelinated afferent-mediated nociception ("first pain") but the summation of small unmyelinated afferent-mediated stimuli ("second pain").

Suprasegmentally, there is well-described tonic inhibition from cortex reciprocally to its thalamic relay nuclei and via the pyramidal tract to presynaptic structures mediating output from lamina IV. Similarly, descending feedback from endorphinergic periventricular and periaqueductal areas through serotonergic fibers in the dorsilateral funiculus of the spinal cord triggers enkephalin-mediated presynaptic inhibition of nociceptor afferent input to laminas I and V (explaining the direct spinal analgesic actions of morphine). Descending noradrenergic fibers appear to participate similarly. These brain-stem pathways are stimulated by ascending nociceptive inputs (negative feedback) and by descending signals relating to stress and other environmental factors.[11]

Alterations Due to Chronic Pain States

When pain has been persistent from any cause, changes may take place in segmental and suprasegmental functions. At the spinal level, the constant bombardment by nociceptive impulses heightens activity in neighboring structures and at near-rostral levels. Central transmission may also be facilitated or disinhibited, as in deafferentation.[12-14] Spillover into the middle and anterior horns tonically heightens outflow to α- and γ-motor neurons and autonomic circuits. The resultant increase in muscle tone and alterations in vasoregulation cause sensitization of nociceptor endings and secondary nociceptive input that change and perpetuate the pain (spontaneous, ectopic nerve impulse generation and secondary myofascial reflex sympathetic overlay). These facilitatory and expanding mechanisms tend to progress rostrally, involving more central levels of the nociceptive pathways and more cephalad segmental structures. After a point, the secondary changes become nociceptive stimuli independent of the original cause of pain, unresponsive to treatments aimed at that original site, and often more difficult to manage (such as phantom pain).

The modulation of input is also disrupted at the segmental, nociceptive level by the above-mentioned facilitation and disinhibition of postsynaptic nociceptive neurons and also possibly at higher centers (long loops) by an increased turnover and depletion of endorphins, serotonin, norepinephrine, or their precursors—leading to a lower threshold for pain perception.[15] Certainly the continuing physiologic stress of chronic pain could affect the systemic (hormonal) opiate effect, mediated by the pituitary-adrenocortical and sympathetic-adrenomedullary axes.

Psychophysiologic studies have not clearly shown changes in patients with chronic pain with respect to their threshold for pain perception.[16] Some investigators have found hypervigilance to signals of somatic distress in patients with chronic pain with a decreased threshold and an increased bias of transmission for pain from any area. Others have found an increased pain threshold, hypothetically due to the "adaptation level" and the influence of past pain experiences and concurrent painful stimuli on perception. (Either pattern could have been influenced by the type of chronic pain studied or nociceptive stimulus used.) By and large, however, patients with chronic pain are at risk to change their approach to the world, even if their threshold for pain cannot be predicted. They may become more somatically oriented, lose a certain amount of insight into the nonsomatic factors affecting their pain, and—in two thirds of cases—become depressed, all of which contribute to irritability, impatience, poor compliance with treatment recommendations, and deteriorating interpersonal relationships with physicians, employers, and family.

When a patient has started on a downward spiral of reciprocating depression and anxiety due to poor responses to treatment and of increasing noncompliance, it becomes more and more difficult for him or her to resume productive relationships at home and at work. Such illness behavior, appropriate only for acute disorders wherein inactivity can be therapeutic, is reinforced by some form of "payoff" (disability payments, litigation-based determinations) or other rewards (narcotic drugs or tranquilizers, increased attention, freedom from onerous tasks or sexual activities), making the behavioral aspects of treatment primary. In fact, in our experience, most failed treatment plans for chronic pain are due to unrecognized or untreatable operant behavioral factors.

When Clinicians Become Part of the Problem

An examiner who does not uncover each component of the nociceptive stimulus, does not work out the natural evolution of a patient's pain, or does not appreciate the psychobehavioral factors involved runs the risk of choosing ineffective or incomplete treatment and of increasing the patient's total disability (Table 3). Secondary myofascial pain or reflex sympathetic dysfunction tends to become worse if not treated specifically. Exploratory operations, lysis of adhesions, resection of scar tissue or "neuromas," more extensive laminectomies and fusions, or other procedures aimed at reducing supposed nociceptive input will have no effect on pain that is already "central" and may add new irritants. Certainly, if an initial surgical procedure is required, prompt postoperative treatment of peripheral neurogenous pain and prompt rehabilitation of soft-tissue structures can often prevent the development of intractable secondary pain syndromes.

The prolonged use of any medication, whether or not a therapeutic effect is sustained, increases the risk of the development of altered cognition or mood and hepatic or renal dysfunction, progressive gastrointestinal dysfunction, idiopathic allergic responses, or drug interactions, not to mention the more serious isolated side effects seen with many of the drugs used for specific types of pain. "Pushing the dose" of any sedating analgesic in an attempt to achieve a better therapeutic response will usually be counterproductive, especially in elderly patients. Nor is it recommended to routinely add

drugs to treat side effects (drowsiness, nausea, itching) of the primary medication before trying a related drug that may be better tolerated. Opiate-class drugs should be used with the awareness that the development of tolerance is typical, necessitating accelerating dose schedules, and that physiologic or psychological dependence may be present after as little as two to six weeks of therapy on a regular dose. An array of unusual medical complications may also be seen with the use of opiates—such as the inappropriate secretion of antidiuretic hormone syndrome, usually with the use of morphine or methadone, and multifocal myoclonus and seizures (from a metabolite of meperidine). Over the long term, the use of narcotics increases albumin synthesis and transiently disrupts the hypothalamic-pituitary axis as well as directly and indirectly altering the response to stimulation-produced analgesia. All these factors lengthen a patient's problem list for the treating physician. On the other hand, phantom limb pain is a more likely consequence of amputation when the presurgical pain was inadequately controlled. We have frequently noted hesitancy on the part of surgeons to prescribe adequate postoperative analgesia for a "chronic pain patient" for fear it could lead to addiction—not being able to separate the acute pain needs from a prior or possible chronic pain problem.

Surgeons are at a special risk when using ablative therapies for persistent pain, as operative lesions in the wrong place along the nociceptive pathways can intensify rather than ameliorate the targeted pain by adding deafferentation factors. A lesion erroneously placed distal to the locus of the facilitated nociception will not alter the more proximally ascending pain. Certainly postcordotomy pain might recur due to the persistence of ascending nociceptive pathways in other cord regions. Even with central stimulation techniques (spinal cord, intracerebral), tolerance can develop despite an initial good response.

Finally, clinicians who never question a patient's requests for medication or disability certification may be perpetuating the chronic illness behavior. If they do not investigate the operant behaviorial factors nor set limits with the patients, based on a realistic assessment of their entire problems, the physicians will be reinforcing inappropriate therapies and leaving themselves open to the increasingly difficult task of justifying—to insurance companies, disability claims examiners, and lawyers—continued treatments.

Evaluating a Patient Who Has Persistent Pain

Isolating the Causes of Pain

The goals of the history and physical examination are to confirm peripheral and central nervous system abnormalities contributing to the perceived pain—including cognitive-emotive dysfunctions—and to confirm the intactness of the nociceptive and modulatory pathways required for treatment.

The patient's history will usually give a clue to the initial triggering factor (infection, injury, surgery) and site of nociception (peripheral receptor, nerve root, visceral organ) that will invariably represent a cause. Over its course, however, the pain will change. With succeeding attempts at operative intervention or just alterations in normal posture—limping, and so forth—myofascial components may increase or spread to neighboring myotomes, with progressive complaints of stiffness, soreness, and sharp, aching, or burning, boring pain, worsened by activity or cold. Central components (severe burning pain) can evolve from an initial neuritic dysfunction or deafferentation (electrical, shooting pains), and there can be an onset of facilitated autonomic discharges, with vasomotor instability and a causalgic overlay. Often these "new" pains are mistaken for a new pathologic disorder, and unnecessary testing or operative procedures will be done.

Patients should be asked to give a numerical value to their pain (on a scale of zero to ten) or to mark on a 10-cm line—a visual analogue scale—the current severity of their pain, with one endpoint representing "no pain" and the other endpoint "the most intense pain imaginable." This can then be reassessed at each succeeding visit.[17] The McGill Pain Questionnaire is also used for serial assessment (Figure 1).[18]

The physical examination should include a complete survey of baseline sensorimotor, circulatory, and skeletal in-

TABLE 3.—*Common Physician Errors in Pain Management*

Missed data	
In history	The use of non-time-contingent analgesics
	Depression or defeatism
	Impatience or noncompliance
	"Doctor-hopping"
	Decreased activity levels
	Excessive family support
	Disability payments or litigation
In physical examination	Scar tenderness (neuromas)
	Myofascial trigger points reproducing pain complaint
	Sympathetic hyperactivity—hypersensitivity, warmth—without inflammation
	Skeletal asymmetry, decreased range of motion, altered gait (postural stressors)
Failure to confirm with diagnostic nerve block	Sympathetic pain
	Central pain versus peripheral afferent-mediated pain
Misuse of medication	Prescribing non-time-contingent analgesics
	Dose too low, dose too sedating
	Giving multiple drugs from same class
	Failing to try non-narcotic classes—nonsteroidal anti-inflammatory drugs, tricyclic antidepressants, anxiolytics
	Failure to try stimulation-produced analgesia
Poor behavioral management	No contract written
	Open-ended treatment plan regarding compliance, goals, ending date
	No attention to behavioral factors, such as depression, low activity levels, operant reinforcements

dices. A more detailed assessment of focal dysfunction in the area of pain complaint should "start from the skin and go in," looking for trophic or vasomotor asymmetries, cutaneous hypersensitivity or denervation, scar tenderness or neuromas, regions of neurovascular entrapment, and myofascial trigger points reproducing any or all of the pain. In addition, differences should be noted in bony symmetry—leg length and so forth—or abnormal gait or range of motion across a joint that could be adding postural stressors to a painful area. Attention, affect, and pain behavior should be noted.

At the conclusion of the history and physical, the examiner should have a clear picture of the areas of somatic or visceral abnormality and their resulting contribution to the overall pain problem. Any doubts about cause or dysfunction should be cleared up with appropriate imaging or electrical studies. A series of diagnostic blocks, obtained through a consulting anesthesiologist, if necessary—myofascial trigger-point injection or manipulation→ peripheral nerve block→ root or facet block→ differential spinal or epidural block, from sympatholytic to somatic sensory and motor blockade—can often dissect out the many overlapping components of a long-standing painful condition.[19] A newer technique, thermography, can show surface evidence of altered sympathetic activity that correlates with an underlying painful condition, the pattern often specific for the nociceptive mechanism—such as radiculopathy, reflex sympathetic dystrophy—but it cannot date the pain problem or give any evidence as to how far rostrally in the pain pathway the dysfunction extends or how severe pain is.[20] Evoked potential research, previewed at the Fourth World Congress on Pain, may, over the next few years, yield standards for determining chronicity and centrality of pain.[21]

Some of the words below describe *today's* pain. Circle only those words that describe it best. Leave out any category that is not suitable. Use only a single word in each appropriate group: the one that applies best.

1	2	3	4
Flickering	Jumping	Pricking	Sharp
Quivering	Flashing	Boring	Cutting
Pulsing	Shooting	Drilling	Lacerating
Throbbing		Stabbing	
Beating		Lancinating	
Pounding			
5	**6**	**7**	**8**
Pinching	Tugging	Hot	Tingling
Pressing	Pulling	Burning	Itchy
Gnawing	Wrenching	Scalding	Smarting
Cramping		Searing	Stinging
Crushing			
9	**10**	**11**	**12**
Dull	Tender	Tiring	Sickening
Sore	Taut	Exhausting	Suffocating
Hurting	Rasping		
Aching	Splitting		
Heavy			
13	**14**	**15**	**16**
Fearful	Punishing	Wretched	Annoying
Frightful	Gruelling	Blinding	Troublesome
Terrifying	Cruel		Miserable
	Vicious		Intense
	Killing		Unbearable
17	**18**	**19**	**20**
Spreading	Tight	Cool	Nagging
Radiating	Numb	Cold	Nauseating
Penetrating	Drawing	Freezing	Agonizing
Piercing	Squeezing		Dreadful
	Tearing		Torturing

Figure 1.—The McGill Pain Questionnaire (from Melzack).[18]

Perpetuating Factors for Pain

Factors that perpetuate pain may be either undiagnosed or incompletely treated nociceptive processes (including missed myofascial syndromes), secondary myofascial or autonomic changes, and postural alterations that stress painful areas. In addition, analgesics may be being used in an inadequate dosage or not time-contingently, that is, taking medications only when pain is severe, hence "rewarding" the pain. Side effects of medication may be interfering with compliance or pain relief, such as when sedating levels of drugs are used during the daytime hours. Signs of anxiety and depression should be noted—difficulty with concentration; changes in sleep pattern, appetite, or sexual activity; tearfulness; mood alteration—and, if severe, the patient should be questioned about suicidal thoughts. Cognitive and behavioral factors are best evaluated by a consultant trained in psychosocial assessment, but clear operants—drug-seeking, disability, litigation, family stability and supports—should be screened for at the initial visit.

Formal Psychological or Psychiatric Evaluation

A psychological or psychiatric evaluation is often sought in multidisciplinary pain management, with the administration of screening psychological tests—Minnesota Multiphasic Personality Inventory, Beck Depression Scale, and other measures of chronic disability—to aid in prognosticating and treatment planning. But even with independent consultation, a premorbid, predisposing, or secondary psychiatric dysfunction may be uncovered that will influence projected somatic therapies, such as a patient being shown to be a poor candidate for invasive diagnostic blocks or ablative procedures or to be seeking passive therapies—drugs, hands-on physical therapies, or acupuncture, to the exclusion of behavioral goals.

Generating a Treatment Plan

The Role of the Contract

For physicians working with patients with chronic, progressive, hard-to-treat problems complicated by behavioral changes and perhaps by negative interactions with other health care professionals in the past, it is important to be clear and specific in laying out opinions, recommendations, and limits to treatment. This is best done in written form, signed and dated by both physician and patient. It should include information about schedules for somatic and behavioral therapies (with the primary physician and possible consultants), medication use, keeping of a daily pain diary during treatment, and the physician's responsibilities regarding disability claims and legal interactions (Figure 2).

Time-limited Goals

All treatment plans should state clear goals with definite ending dates for assessment, such as reducing pain by 50% over the first six weeks, return to work part-time by a specific date (month, day, and year), and comprehensively reevaluate during a specific week. A patient compliant with the treatment plan who fails to meet these goals can thus be recognized earlier as being in the wrong combination of treatments or the wrong setting—outpatient versus inpatient—and ad-

justments made. A noncompliant patient can be challenged to the contract and terminated from continuing treatment, if compliance issues cannot be resolved.

Medication Management

Analgesic drugs should always be prescribed on a time-contingent basis, as round-the-clock medication maintains pain at a tolerable even level and can decrease the total amount of drug required over 24 hours. The use of simpler drugs, such as aspirin or acetaminophen, should be maximized by increasing dose strength or frequency before switching to stronger or narcotic alternatives. Mixing several drugs from similar classes should be discouraged. On an outpatient basis, oral or rectal administration is preferred, and when changing from one narcotic to another of a different route, equivalent analgesic doses should be calculated.[3] Parenterally given narcotics do have a more rapid onset of effect but a reduced duration of action, and tolerance to them develops quicker.

Date _____

I, _____, understand that to properly manage my pain problem, the following time-limited treatment plan has been specifically designed for me:

1. Home program—consisting of exercises, increased awareness of posture and general body mechanics, and practicing relaxation and stress management skills six times a day.
2. Physical therapy—twice a week for six consecutive weeks.
3. Relaxation and stress management one session a week with Dr _____ for six weeks.
4. Regular follow-up visits with Dr _____ once a week until reevaluation. As treatment progresses, other treatment modalities such as spray and stretch, trigger-point injections, or acupuncture may be added if deemed necessary.
5. I will keep (hourly, daily) diaries of my pain levels, activities, and medication use throughout my course of treatment.
6. Medication management:
   I understand that to properly manage my pain problem, and to help me reduce and eliminate my medication intake, the following medication regimen will be instituted:
   (a) I must take my medications on a time-contingent basis . This means that I will take my pain pills as prescribed by the clock (for example, one Tylenol #3 at 8 AM, 2 PM, and 8 PM; no more, no less) and not according to how I feel.
   (b) I understand that I will be given just enough medication to last until my next appointment and no more . Should I lose a prescription or the medications or should I take more than prescribed for any reason, I understand that my prescription will not be refilled until the agreed-upon time.
   (c) As treatment progresses, the above dosage will be systematically decreased within the limits of my comfort. I understand that my cooperation is essential.
   (d) I will not make Emergency Department visits for any injectable analgesics.

I understand that the home program is the most important and that without following through with this, I can expect little or no improvement in my pain.

Reevaluation will be scheduled for the week of _____. If little or no improvement has occurred by this time, I understand I may be terminated as a patient at that time.

Letters for attorneys, insurance companies, disability should be requested at the time of this treatment planning session.

Figure 2.—A sample is given of a treatment contract to be entered into by a physician and patient for the management of pain.

Adjunctive drugs include those specific for the cause or origin of the pain, such as phenytoin, carbamazepine, or baclofen for some central pain, trigeminal neuralgia, postinfectious or traumatic neuralgias, or painful peripheral neuropathies; nonsteroidal anti-inflammatory drugs or muscle relaxant preparations for acute or chronic soft-tissue or muscle changes; and antispasticity or basal ganglia-focused drugs to diminish centrally generated, painful increases in tone. Continued research on the peripheral mediators of pain (substance P, leukotrienes) may yield additional drugs with the same efficacy as the antiprostaglandin effects of the nonsteroidal anti-flammatory drugs.[22,23] D-Phenylalanine, a carboxypeptidase A inhibitor, may increase central enkephalin levels in primates and, hence, may be a useful adjunct to therapies aimed at increasing endogenous opiate release, such as stimulation-produced analgesia.[24] The descending serotonergic pathways may be stimulated by the use of tryptophan (2 to 3 grams at bedtime with a carbohydrate snack) or the tricyclic antidepressants, specifically amitriptyline hydrochloride or doxepin hydrochloride (100 to 200 mg at bedtime).[24]

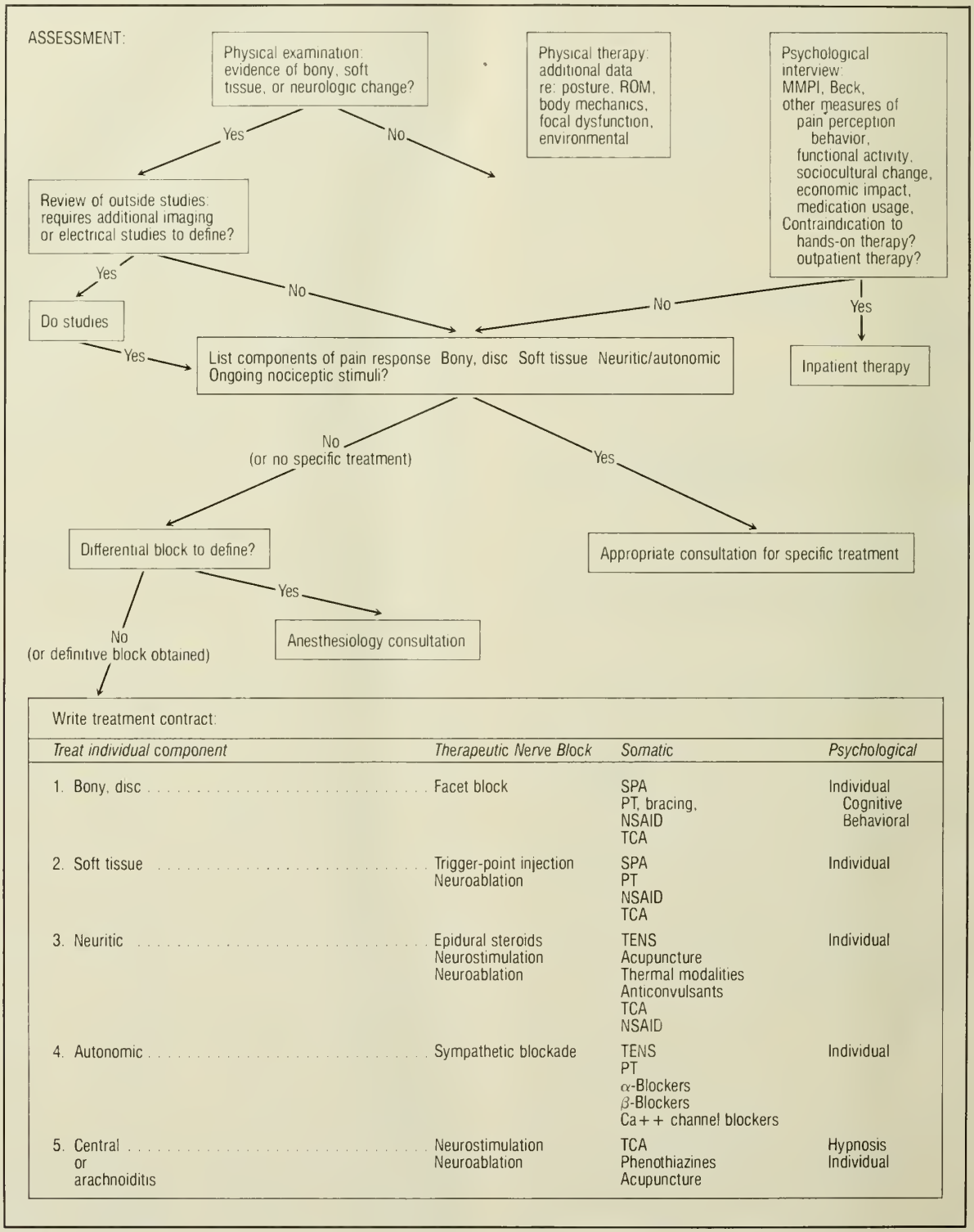
Patients should ideally receive all their pain-related medications and certainly all their narcotics from only one practitioner. A patient who will require habitual narcotic medication should be registered with the state drug enforcement agency as being under that physician's care. If narcotic use is no longer desired, tolerance, dependence, and detoxification can be managed on an outpatient basis by slowly tapering the dose of the narcotic or switching it to an equivalent analgesic "pain cocktail" from which the narcotic is slowly eliminated—such as by lowering the dose by 10% per week. The narcotic therapy can be abruptly discontinued and clonidine used (0.1 mg orally three times a day for up to three weeks) to cover withdrawal signs and symptoms.[26] (Electroacupuncture has also been used for this purpose.[27]) These more abrupt techniques may be best tried on an inpatient basis.

Nondrug Techniques for Altering Pain Perception

Experimental studies in animals and humans[11] suggest that there are four basic classes of analgesia: (1) neural-mediated opiate, such as systemic, epidural, and intrathecal administration of morphine, and deep brain stimulation; (2) hormonal opiate, dependent on pituitary adrenocortical or sympathetic adrenomedullary axes, such as acupuncture; (3) neural-mediated nonopiate, perhaps serotonergic, such as brain stimulation; and (4) hormonal nonopiate, such as various environmental stressors. The clinical use of these "stimulation-produced analgesias" has been increasing, especially with the growing governmental regulation and acceptance of acupuncture-related therapies—traditional acupuncture, electroacupuncture, percutaneous electrical nerve stimulation, and auriculoacupuncture. Unfortunately, due to cross-tolerance, patients receiving high doses of narcotic drugs may not respond well to acupuncture techniques unless detoxified. Similarly, prolonged steroid use may suppress endogenous endorphins and make their acupuncture-stimulated release less effective. Transcutaneous nerve stimulation (TENS) appears to act through both opiate (low frequency, high intensity) and nonopiate (high frequency, low intensity) pathways, possibly influencing segmental inhibitory mechanisms, but not clearly through the same mechanisms as acupuncture. TENS may have beneficial effects on circulation as well. Various forms of therapeutic counterstimulation have been present in the folk medicine of all cultures, and, as such, TENS

research may yield the important unifying factors relating them to the known analgesic systems.

When choosing a therapist to provide acupuncture treatment or TENS instruction to a patient, it is important to seek out licensed practitioners familiar with the disease state under question and willing to work closely with the referring physician. Physical therapists often use TENS, but may limit themselves to only one mode (high frequency, low intensity) that may not be the best choice for all patients. The clinician should monitor the patient's ability to work with a TENS unit, if prescribed for home use. He or she should also oversee the response to acupuncture; with an average of two treatments per week, some response should be seen by the third week. Maximal response is usually reached by 18 to 20 treatments and maintained for three to six months, after which a shorter "booster" course may be given (often required for the man-



Treat individual component	*Therapeutic Nerve Block*	*Somatic*	*Psychological*
1. Bony, disc	Facet block	SPA PT, bracing, NSAID TCA	Individual Cognitive Behavioral
2. Soft tissue	Trigger-point injection Neuroablation	SPA PT NSAID TCA	Individual
3. Neuritic	Epidural steroids Neurostimulation Neuroablation	TENS Acupuncture Thermal modalities Anticonvulsants TCA NSAID	Individual
4. Autonomic	Sympathetic blockade	TENS PT α-Blockers β-Blockers Ca++ channel blockers	Individual
5. Central or arachnoiditis	Neurostimulation Neuroablation	TCA Phenothiazines Acupuncture	Hypnosis Individual

Figure 3.—The diagram represents a "decision tree" for low-back pain. MMPI = Minnesota Multiphasic Screening Inventory, NSAID = nonsteroidal anti-inflammatory drugs, PT = physical therapy, ROM = range of motion, SPA = stimulation-produced analgesia, TCA = tricyclic antidepressants, TENS = transcutaneous electrical nerve stimulation

agement of chronic arthritis, postherpetic neuralgia unresponsive to nerve block or medication, pain from nerve or root injury or arachnoiditis, and some forms of central pain).

Rehabilitation

The role of soft-tissue or muscle factors in altering and extending a primary pain problem, making it more resistant to treatment—or mimicking it altogether—cannot be overemphasized. A physical therapy evaluation should be included in all treatment plans, and those recommendations adhered to (often for periods of time well exceeding the baseline, time-limited contract). Occupational therapy, vocational rehabilitation, work-hardening programs, and longer-term psychosocial intervention may also be appropriate. The patient may continue to experience pain but ultimately should be better able to cope with it and to suffer less disability in daily life because of it.

Psychological Techniques

The behavioral techniques of limit-setting, specific goal achievement, and contingency planning should be part of any treatment plan, even when the support of a psychosocial therapist is not available. The physician will focus these at pain behavior, medication usage, and physical disability, although job-oriented or family-related goals may also be included, the aim being to make patients more responsible for their own care and to reward "well behavior" (increased activity and decreased drug intake).[28] Through contacts with mental health professionals skilled in stress management, relaxation training, or biofeedback for muscle relaxation, these modalities can be mobilized. Hypnotic analgesia is not mediated by endogenous opiates, although placebo analgesia may be.[11]

Inpatient Versus Outpatient Settings

When the medication usage is prohibitive or parenteral drugs are involved, when outpatient behavioral techniques are ineffective in altering the more serious pain behaviors, or when somative rehabilitation needs are too great, a limited (four to six week) hospital stay, with care designed for pain management, may be more effective than the most rigorously structured outpatient program.[29] The services offered by available inpatient programs—and multidisciplinary outpatient programs—should be weighed relative to an individual patient's needs before referral. Some groups focus heavily on diagnosis and somatic treatment, others on rehabilitation, and still others on medication elimination and behavioral modification. A patient may fail in one program type but do very well in a program of a different focus, so the correct choice made early can save money and time for all involved.

When Is Surgical Treatment Appropriate?

If there is clearly remediable disease that relates directly to an ongoing nociceptive stimulus—and diagnostic neural blockade shows that all the pain experienced is coming from that site—removing the irritant could be curative, provided postoperative soft-tissue rehabilitation is not overlooked. Therapeutic neural blockade is essentially an operation done with needles and is used in the nonoperative treatment of facet and disc syndromes. Repeated reversible sympathetic blockade can be effective treatment for primary, secondary, or neuroma-mediated reflex sympathetic pain.[30] Permanent nerve blocks are a form of ablative surgery and should be reserved for carefully defined clinical situations, such as a celiac plexus block for intractable abdominal pain of malignant origin. Invasive stimulation techniques (spinal cord and intracerebral) can be helpful when less invasive treatments have failed, but the behavioral and psychological aspects of a patient should be well assessed as a part of gathering the data required to make those therapeutic recommendations.[31] An intravenous morphine test should be part of the presurgical evaluation to establish opiate sensitivity of the pain.

Once pain has been present for longer than six months, it is unlikely that there will be a single, as-yet-untried "cure." For success in modern pain management, all the factors of somatic, psychiatric, and behavioral input to chronic pain need to be recognized and addressed as a unit (Figure 3). Clinicians should integrate their particular skills with those of reliable outside consultants and programs to bring the clearest picture and most realistic treatment plan to patients suffering from persistent pain.

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Cystic Fibrosis

Discussants
IVAN HARWOOD, MD; FERNANDO ROSAS, MD; DAVID K. EDWARDS, MD; JOHN KELSO, MD; *and*
WILLIAM L. NYHAN, MD, PhD

IVAN HARWOOD, MD:* A starting point for the discussion of important topics in cystic fibrosis and its management in infants is provided by an informative case of a patient, which will be presented by Dr Rosas. From there we will discuss the rapidly developing advances in diagnosis and therapy.

Case Presentation

Case 1

FERNANDO ROSAS, MD:† The mother was seen because of polyhydramnios and other factors that led to the decision to deliver the infant at 33 weeks by cesarean section. She was 30 years old and the father 39. The first of five siblings died at the age of 15 months of what was called intestinal infection, the fourth was a fetal death at 20 weeks of gestation, and the fifth died at 3 months of age of pneumonia. This pregnancy had been complicated by a culture positive for herpesvirus three months before delivery. A sonogram one week before delivery showed massive hydramnios. A screening test for toxoplasmosis, rubella, cytomegalovirus (CMV), and herpes (the "TORCH" screen) indicated a greatly elevated level of type II herpesvirus immunoglobulin and a mildly elevated type I, as well as substantially increased CMV titers. The culture for CMV was negative.

At birth the infant was found to have a very distended abdomen. X-ray films showed diffuse calcifications essentially diagnostic of meconium peritonitis. He was taken to surgery for an exploratory laparotomy and lysis of adhesions. There was diffuse meconium staining, but no perforation was found. Postoperatively he did well and was discharged at 18 days of age. His weight at that time was 2.14 kg.

During a month at home he had more or less continuous diarrhea. Three changes of formula from breast milk to Isomil Soy Protein Formula With Iron (Ross Laboratories) to Similac With Iron Infant Formula (Ross) to ProSobee (Mead Johnson Nutritional Division) were without major effect. Two weeks after discharge his weight was 2.19 kg. One month after discharge he was seen in the emergency department where he was described as flaccid and appearing ill. He still had diarrhea and his weight was 2.44 kg. There were expiratory wheezes, occasional rales, and slight stridor. He was admitted and treated with a regimen of ampicillin and gentamicin sulfate. His respiratory status deteriorated despite the use of antibiotics and the addition of aminophylline. He was found to have a partial oxygen pressure of 31 torr and a partial carbon dioxide pressure of 52 torr, and it was decided to insert an endotracheal tube for ventilation and to begin treatment with ribavirin. *Klebsiella* and *Escherichia coli* were found on tracheal culture.

His course was stormy because of recurrent episodes of increased airway resistance and increased difficulty in ventilation, but his condition slowly improved, and the endotracheal tube was removed about a week later. His weight was 2.3 kg. At 2 months of age, sufficient sweat could be collected for the first time for a sweat test, which was positive; the chloride concentration was 95.7 mEq per liter and the specimen weighed 130 mg.

Six weeks after admission, he was discharged weighing 2.7 kg and tolerating Pregestimil (Mead Johnson) formula supplemented with glucose polymers (Polycose [Ross]) to provide 238 calories per kg per day. He was readmitted four days later with pneumonia, respiratory distress, and diarrhea and was treated with a regimen of tobramycin and piperacillin sodium.

Response was rapid, and he was discharged 2½ weeks later. At 4 months of age his weight was 3.65 kg. At 6 months of age, he was readmitted because of increased cough, wheezing, and the production of sputum. A sputum culture showed *Staphylococcus aureus* and *E coli*. He again responded to treatment with tobramycin and piperacillin and was discharged after three weeks, receiving cephradine and sulfamethoxazole-trimethoprim (Septra).

His most recent outpatient visit was at 7 months of age. He was generally stable and weighed 5 kg, but he had a chronic cough productive of clear, thick sputum.

DR HARWOOD: Thank you, Dr Rosas. Dr Edwards will describe the x-ray findings.

Radiologic Findings

DAVID K. EDWARDS, MD:* Prenatal sonography done six days before delivery showed moderate hydramnios (Figure 1). There was also evidence of fetal ascites and thickening of the abdominal soft tissues, findings that are suggestive of nonimmune hydrops but in this case are probably a consequence of fetal peritonitis. Ultrasound is generally relatively insensitive to calcifications; in any event, no intra-abdominal calcifications were noted either at the time of sonogram or retrospectively.

Following delivery, plain radiography showed scattered

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ABBREVIATIONS USED IN TEXT

CF = cystic fibrosis
CMV = cytomegalovirus
PON = paraoxonase
RFLP = restriction fragment length polymorphism
UCSD = University of California, San Diego

flecks of intraperitoneal calcification, findings virtually pathognomonic of meconium peritonitis. It is our practice in such cases to seek the approximate site of perforation with an upper gastrointestinal tract examination using a nonionic water-soluble contrast material (Figure 2). In the infants in whom the perforation is still patent at delivery, this technique often gives a surgeon a clue as to where the perforation is situated and at the same time excludes atresias, severe stenoses, malrotation, and other abnormalities that may be associated with meconium peritonitis.

The scout film showed pneumoperitoneum, implying postnatal patency of the perforation, but the examination with contrast material failed to show leakage into the peritoneum. It was professionally consoling that the surgeons similarly failed to find a leak. The leak had evidently closed spontaneously.

Chest radiographs during the child's subsequent period of severe respiratory illness revealed shifting patches of atelectasis, areas suggesting pneumonia, and miscellaneous complications related to endotracheal intubation. Following recovery, his chest films have become fairly typical of children of this age with cystic fibrosis, showing mild hyperinflation and peribronchial thickening (Figure 3).

Discussion

Dr Harwood: Thank you, Dr Edwards. This patient had meconium peritonitis, a prenatal consequence of cystic fibrosis. In about half the cases, the meconium peritonitis is due to the meconium ileus of cystic fibrosis and in about half it is due to all the other causes of intestinal obstruction in a fetus, including malrotation and valvular stenosis and atresia. Virtually all patients who have meconium peritonitis with meconium ileus have cystic fibrosis. Therefore, a diagnosis of meconium ileus is a presumptive diagnosis of cystic fibrosis.

Some 10% to 12% of patients with cystic fibrosis are born with meconium ileus. On examination during a surgical pro-

Figure 1.—A prenatal transverse sonogram of the fetal abdomen shows abdominal wall soft-tissue thickening **(solid arrows)** and ascites **(white arrow)**.

Figure 2.—The photo shows the final film from an upper gastrointestinal series with nonionic water-soluble contrast material; no intraperitoneal spill of contrast material was observed. The arrows indicate calcifications of meconium peritonitis.

cedure, the typical appearance of meconium ileus is of dilated proximal loops and a dark, small, congested, and obstructed distal segment.

A few infants with meconium ileus experience spontaneous relief of the obstruction. Most require other measures. In less than half, the obstruction can be relieved by an enema with *N*-acetylcysteine or diatrizoate meglumine (Gastrografin). Most require surgical relief of the intestinal obstruction. In this patient, no site of obstruction or continuing leak was found at exploration. This case shows that there may be other complications associated with meconium ileus prenatally or postnatally, such as perforation and peritonitis. The distinctive meconium in meconium ileus is dehydrated, tarry, and very sticky, and it has a high protein content. It is easy to understand why this material causes obstruction.

Infants presenting with severe manifestations of cystic fibrosis so early in life have a high mortality rate, as much as 30% within two months of birth. There are four reasons for this high rate. One is the higher incidence of prematurity in this group. Other abnormalities in the gastrointestinal tract are common, as is severe malnutrition, seen in the hypoproteinemia anemia syndrome. Finally, and very important, is the high risk of early and severe pulmonary disease developing, manifested by prolonged bronchopneumonia and bacterial bronchiolitis.

We have another illustrative case, which will be presented by Dr Kelso.

Case 2

John Kelso, MD:* This patient was born after 38 weeks' gestation, weighing 2,860 grams. Pregnancy, labor, and delivery were uncomplicated. The baby was discharged to home on day 2, but was readmitted on day 3 because the serum bilirubin level had risen from 11.2 to 16 mg per dl. The direct fraction was zero.

Breast-feeding was discontinued for 48 hours, and phototherapy was initiated. The baby's hematocrit was 51%. The baby was treated, the bilirubin level fell to 8.2 mg per dl in three days, and the mother resumed breast-feeding. Weight gain was poor; the baby spit up after most feedings. A roentgenogram taken after the patient swallowed barium was completely normal.

At 2½ months of age the baby presented with fever and irritability and was admitted for investigation of sepsis. Cultures were negative, but the hematocrit was 21.6%. The weight was 3.7 kg. The red cell indices were normal, the leukocyte count was 4.5×10^3 per μl, and the platelets 411,000 per μl. There was no evidence of hemolysis or gastrointestinal bleeding. The baby was transfused and the hematocrit rose to 33%.

Three weeks later the hematocrit was down to 25% and the baby had lost 0.45 kg. He weighed 3.62 kg at 3 months of age. In addition, on physical examination there was pretibial edema and the liver was palpable 2 cm below the costal margin. Following admission the alkaline phosphatase level was elevated, as was the γ-glutamyl transferase value. The serum aspartate aminotransferase (glutamic-oxaloacetic transaminase) and serum alanine aminotransferase (glutamic-pyruvic transaminase) levels were normal. The serum albumin value was 2.0 and the total protein 3.4 grams per dl. The baby's sweat chloride concentration was 105 mEq per liter. A diagnosis was made of cystic fibrosis.

The patient has done well since. The administration of pancreatic enzyme was started, and following a transfusion he was able to maintain his hematocrit and serum protein concentrations; the edema disappeared. To this point he has not shown any evidence of pulmonary disease. The chest roentgenogram was normal.

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Figure 3.—A chest radiograph taken at 6 months of age shows mild hyperinflation and peribronchial cuffing.

Diagnosis and Treatment

Dr Harwood: Two things that happen with significant regularity to infants with cystic fibrosis can be at least partially prevented if treated presumptively. These are the hypoproteinemia syndrome and the severe and frequently fatal form of lung disease that affects these infants in the first year of life. Our second patient presented with anemia and was found to have edema and a serum albumin concentration of 2 grams per dl. Most patients with this syndrome present with generalized edema, suggesting the differential diagnosis of the nephrotic syndrome or protein-losing enteropathy. This syndrome of hypoproteinemia, edema, and anemia occurs mostly in patients with cystic fibrosis between 1 and 4 months of age, with a few instances of presentation between 4 and 8 months of age. This syndrome may occur in as many as 5% to 10% of infants who become ill in the first three months of life. Symptoms have usually been present for four to eight weeks before the diagnosis is made.

One of the important factors in prevention is the recognition that most infants in whom this syndrome develops have received soy-based formulas or breast-milk feedings. Soy protein seems to be of poorer quality with poor absorption in cystic fibrosis, which only improves to fair absorption with pancreatic enzyme replacement. Breast milk is qualitatively good, but there is simply not enough protein in breast milk to compensate for the malabsorption in these infants. The formulas based on cow's milk provide fair to good protein absorption even without enzymes, and this improves with pancreatic enzyme replacement.

Hypoprothrombinemia also occurs in patients with this syndrome. This is a consequence of a deficiency of vitamin K, which is thought to occur because of the relatively low content of dietary vitamin K, the frequent use of antibiotics in these infants, and the malabsorption. Deficient protein synthesis may play a part in this as it does in the hypoalbuminemia. The prothrombin time and the partial thromboplastin time may be prolonged. Infants who have hypoprothrombinemia may pre-

sent with bruising, hematemesis, or bleeding at sites of injection, venipuncture, or heel or finger puncture.

A grossly edematous infant with the hypoproteinemia syndrome of infantile cystic fibrosis is shown in Figure 4. An infant who was less edematous but who had multiple bruises on his head and on his back is shown in Figure 5. Both infants were evaluated for renal disease, and the second was referred as a battered child before the correct diagnosis was made.

Prevention or treatment of this syndrome is dependent on an early diagnosis. The first step is pancreatic enzyme replacement. As soon as a baby is diagnosed as having meconium ileus or has a positive sweat test, treatment with enzyme replacement should be started, and an appropriate high-protein formula, usually Pregestimil or a cow's milk formula, be given. It is possible for some of these infants to continue breast-feeding with enzyme replacement, particularly if the mother is willing to supplement the breast milk with some cow's milk formula. For a sick hypoproteinemic infant, parenteral administration of albumin and fresh frozen plasma may be useful supportive measures in the initial stage of therapy.

Because of the severe malnutrition that characterizes this syndrome, these infants are at high risk for fatal infections such as severe pulmonary infection or sepsis. Our practice is to be aggressive in resorting to antibiotic therapy at the first sign of pulmonary infection in these infants, as they seem to get sicker and stay sick longer than other infants of the same age with cystic fibrosis who do not have hypoproteinemia.

Figure 4.—The photo shows an infant with cystic fibrosis who presented with gross edema and hypoproteinemia.

Figure 5.—Another infant is shown with cystic fibrosis who had somewhat less edema, but he also had multiple bruises as a result of hypoprothrombinemia.

Another presentation of cystic fibrosis in infancy is metabolic alkalosis.[1] An infant may present with failure to thrive, lethargy, or signs of dehydration without a history of diarrhea or vomiting. Anorexia is a regular concomitant. This presentation is particularly common in warm weather when rates of sweating increase. The electrolyte analysis reflects a typical hypochloremic alkalosis in which the bicarbonate value is high and the chloride level low. As compensation fails, the pH rises. These infants also frequently have hyponatremia and hypokalemia. The differential diagnosis includes pyloric stenosis, intoxication with exogenous alkali, juxtaglomerular cell hyperplasia (Bartter's syndrome), and hyperaldosteronism.

A most important issue for clinicians is the very different presentation of pulmonary infection in infants with cystic fibrosis who are younger than 1 year. The pattern of lung infection in infants is a bronchiolitis-like syndrome that often cannot be distinguished clinically from viral bronchiolitis. Affected infants have the clinical manifestations of a severe bronchiolitis, such as coughing, wheezing, cyanosis, and hypoxemia. There most often is a failure to thrive, and these infants are significantly malnourished even if there is no overt malabsorption. The lungs of these babies are characterized by hyperinflation, often severe enough to cause respiratory failure.

This syndrome occurs primarily in infants younger than 9 months, and its incidence is skewed towards the younger end of the age group. The course of illness is usually prolonged. The cough tends to be wheezy rather than productive. Treatment may take many months of administering antibiotics intravenously even when the organisms are identified and are sensitive to the antibiotics being given. The predominant organisms cultured from infants with this syndrome are *Pseudomonas aeruginosa, Klebsiella pneumoniae,* and *E coli.* Seen less frequently are *Staphylococcus aureus* and *Candida albicans.* In our experience, *K pneumoniae* is the most common organism found in these young infants. In the second patient discussed, the initial cultures contained *Klebsiella* as the only pathogen. Later he was colonized by *E coli,* and his last sputum culture contained *S aureus,* which led to his treatment with a cephalosporin and its successful eradication. His cultures will undoubtedly become positive for *P aeruginosa* in the future and, once colonized with that organism, he will essentially carry it for the rest of his life.

The prognosis used to be grim for these infants, with about 30% dying in the acute episode and as many as 50% dying within two months. Experience in recent years has been much better than that, reflecting an improved antibiotic armamentarium, earlier diagnosis, and a more aggressive management.

These are indeed desperately ill infants. If they can survive this initial phase of the illness, however, most of them have a stable course and do quite well, such as an infant who was admitted to hospital for three months at 3 months of age in respiratory failure. He had *Pseudomonas* bronchiolitis and was discharged home at 6 months of age still in respiratory insufficiency. Thirteen years later, he has not required a single admission to hospital, has normal pulmonary function, a relatively clear chest x-ray film, and he lives a normal life for someone his age.

Pathophysiology

Consideration of the pathophysiology will provide some insight into why these infants act the way they do and how best to manage them. Most of the functional derangement is a consequence of partial obstruction and air trapping in the terminal airways and alveoli. There are relatively little destruction and bronchiectasis seen in these infants. Later, as the lung disease progresses, there are increasing obstruction, atelectasis, bronchiolectasis, small and large abscess formation, and bronchiectasis. Because this obstruction of the small airways is inflammatory rather than bronchospastic, bronchodilators are of little benefit. A few infants who have an added component of bronchoconstriction may respond to bronchodilators.

Postmortem examination of the lungs shows massive hyperinflation. The lungs do not deflate even after the chest has been opened. The lungs may be almost normal in appearance on the surface, and there may be no gross evidence of atelectasis or pneumonia. On microscopic examination there is amorphous material partially or completely plugging every identifiable airway, while the alveoli, although expanded, usually have a normal structure.

This is one of the wheezing disorders that must be treated with antibiotics. Usually prolonged administration is required of parenteral agents such as aminoglycosides, semisynthetic penicillins, and third-generation cephalosporins active against *Pseudomonas* and *Klebsiella*.

Infants known or suspected to have cystic fibrosis should have baseline and periodic cultures of their respiratory tract flora so that immediate and aggressive antibiotic therapy including parenteral antibiotics can be started at the first sign of small airway obstruction. This aggressive approach to therapy will in many cases prevent progression of the disease and respiratory failure requiring ventilator therapy. An aggressive approach seems to reduce the high mortality for this high-risk group of infants.

Review of the family history of the first patient presented strongly suggests that two siblings died in infancy of cystic fibrosis. It is worthwhile to review the symptoms suggestive of cystic fibrosis in infancy in addition to meconium ileus (Table 1). The sweat test should be done on any infant with recurrent or prolonged respiratory symptoms, such as cough or production of sputum, as well as radiographic signs of infection. It should also be done on infants with unexplained failure to thrive and chronic or recurrent intestinal symptoms. Infants with hyponatremia or metabolic alkalosis with hypochloremia should be tested, as well as those with edema, hypoproteinemia, or a family history of cystic fibrosis. Parents are being alerted that an infant who tastes salty when kissed should be brought in for testing. Less common presentations are hyponatremic dehydration and heat stroke. Less specific presentations are with prolonged neonatal jaundice, inguinal hernia or hydrocele, and the absence of the vas deferens.

The sweat test is still the diagnostic test of choice for cystic fibrosis. The test is conceptually simple but practically difficult to do consistently and accurately. The standard Gibson-Cooke method,[2] in which pilocarpine iontophoresis is followed by quantitative analysis of the chloride content of the sweat specimen, is the most accurate method. The range of sweat chloride levels in normal persons is from 10 to 60 mEq per liter. Carriers are not different. The population of patients with cystic fibrosis have chloride values from 60 to 160 mEq per liter. There is virtually no overlap with normal values. There are a few patients who consistently have sweat chloride values in the 40- to 65-mEq-per-liter range who have some of the abnormalities seen in patients with cystic fibrosis. A decision as to whether to label such a patient as having cystic fibrosis depends on the number and intensity of the other stigmata present and the judgment of an experienced clinician. As shown in the patient presented, it may not be possible to obtain a positive diagnosis by sweat test in a very young infant, simply because one cannot obtain a sweat specimen.

The genetics of cystic fibrosis are those of a classic mendelian autosomal recessive disorder. The incidence of heterozygotes in the population who are clinically normal but carry the gene is about 1 in 20. The frequency of union of two heterozygotes is about 1 in 400, and the frequency of the birth of a homozygous affected person is about 1 in 1,600 to 1 in 2,000. The gene is expressed only in the homozygous state. The sexes are affected equally. There is no effect of maternal or paternal age or birth order. Consistent with the status of cystic fibrosis as a common recessive disorder, consanguinity is not frequently encountered in affected families, although consanguinity will increase the chances of transmission of any autosomal recessive disease. This gene has its highest frequency in northern European populations, but is still quite common in middle and southern Europe and, of course, in the United States. It is about five times less common in the black population of the United States and is rarely seen in Asians. Because of our experience as a border town in San Diego, we have suspected that the gene is relatively common in Mexico, but there are insufficient epidemiologic data to corroborate this suspicion. The prevalence is not known in Central and South America.

I would like to describe a new project that will enhance the body of information about cystic fibrosis, the Western Consortium CF Database. This is a collaborative project of 16 major cystic fibrosis centers in California, Washington, Arizona, and New Mexico. Currently more than 1,600 patients are entered into the computerized data base. In these centers every patient visit is recorded on a common clinical visit form that is forwarded to the central computer, and about 60 items of information are recorded in the computer about that pa-

TABLE 1.—*Symptoms Suggestive of Cystic Fibrosis*

Persistent cough
Recurrent pneumonia
Recurrent atelectasis
Emphysema
Wheezing
Hemorrhagic tendency
Failure to gain weight
Steatorrhea
Jaundice
Low salt syndrome
A sibling with cystic fibrosis
Vitamin A deficiency
Meconium ileus
Intestinal obstruction
Rectal prolapse
Edema
Hypoproteinemia
Salty skin

tient, such as height, weight, pulmonary function, microbiology, and antibiotic and other drug use. It is now possible to characterize this large population of patients and to characterize the different centers as to types of patients and type of treatment provided. We can examine current practices and compare the efficacy of clinical care and the outcome between different centers. It is possible to correlate various measurements such as clinical score and pulmonary function with other outcome measures, including morbidity and mortality. An important feature is that we can now quickly and precisely define a subgroup of patients for prospective clinical studies. This program, started less than a year ago, has now reached the point where it is clinically useful. We are very excited about the potential of this new tool for improving the care of our patients.

We turn now to Dr Nyhan, who will consider the rapidly evolving field of cystic fibrosis genetics and current capabilities for prenatal diagnosis and heterozygote detection.

Molecular Genetics of Cystic Fibrosis

William L. Nyhan, MD, PhD:* New techniques of molecular biology have provided exciting inroads into the fundamental nature of cystic fibrosis. The application of properties of recombinant DNA and the emerging tools of molecular genetics have permitted the precise localization of the gene for cystic fibrosis to the long arm of chromosome 7. This precise mapping, and the close linkage to readily determined markers, has provided the means for early diagnosis, including prenatal diagnosis, and for heterozygote detection.

While we have no idea what this gene codes for, we can use its location in these very practical ways to achieve clinical objectives. This situation typifies the exploding new area of molecular genetics, an offshoot that some of us have called reverse genetics. In the first applications of molecular biology to medicine—the forward or straightforward genetics—genes were cloned because their protein structure was known or because properties of those proteins were known, such as the behavior of cells in selective media depending on whether the activity of that enzyme protein was present or not. Examples include the cloning of the β-globin gene or the hypoxanthine guanine phosphoribosyl transferase gene. Other examples are, of course, the development of drugs from cloned human genes, such as insulin or growth hormone. These have all been notable successes.

At the same time, it was recognized early that the vast majority of genes that cause human disease are not available to this direct approach, as there is no known enzymatic or other gene product that marks the normal gene, indicates its function, or delineates the variation that causes the disease. It is to these disorders that the new, less direct approaches have been made to identify a gene by finding its location on a chromosome and by identifying molecular markers that are so close to the gene that recombination is an unlikely event. Then the marker can be used to identify the gene. This is the logic that has permitted the identification of markers for cystic fibrosis and for Huntington's disease, for which no candidate genes were known before the search was undertaken. The logic also stipulates that if the region of a gene can be defined closely enough through linked regions, then the underlying gene can be identified and cloned. This logic has been amply justified by the isolation this year of the genes for retinoblastoma, chronic granulomatous disease, and Duchenne-type (pseudohypertrophic) muscular dystrophy.

The technology depends on the ability to split long molecules of deoxynucleic acid into many small fragments by the action of restriction endonucleases, each of which acts to cleave the DNA at a very specific site that is determined by the sequence of nucleotides (Figure 6). Once the fragments of various sizes are obtained, they are separated by electrophoresis in agarose gels. They are then transferred to membranes where the various fragments can be recognized by hybridization to highly specific probes, pieces of DNA labeled with phosphorus 32, so they can be found autoradiographically, after they have sought out and bound to strands of DNA that have nucleotide sequences to which they are complementary. The gel is then developed like an x-ray film and the pattern of fragments of various molecular sizes bound to the probe examined. If a normal gene contains a site that is cleaved to yield a small fragment to which the probe binds—and in a disease the gene is altered so that this site is missing, a situation that could result from a big, even visible deletion or a single base change—then the enzyme will not cleave to produce the small fragment that will be missing on the resultant gel, and a new larger fragment will appear. These techniques have shown that there is a great amount of polymorphism in human DNA, even among normal persons. Differences identified in this way are known as restriction fragment length polymorphisms, or RFLPs. It was recognized early that this polymorphism could be used in the linkage analysis of human disease. Thus, in its first application it became possible to do prenatal diagnosis for sickle cell disease long before the specific approaches to the altered site that are now used for this purpose became available. It has since been applied to the prenatal diagnosis of a number of diseases such as phenylketonuria and the Lesch-Nyhan disease, in which patients generally do not have a pattern that is any different from those of normal persons. RFLPs that can be detected with a complementary DNA probe made from the gene for the normal enzyme are so closely linked that they can be used to trace the gene in families that are suitably informative, in that the carriers are heterozygous for the marker in question.

In the approach to the cystic fibrosis locus, some 200 RFLP markers were studied for linkage in 39 informative families in which there were two or more patients with cystic fibrosis and with parents available for study. One of these,

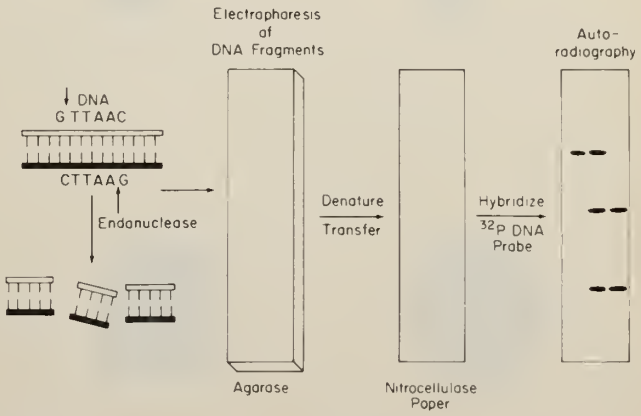

Figure 6.—The schematic representation shows the use of a restriction endonuclease and a specific complementary DNA probe to identify restriction fragment length polymorphism that can be linked to a specific gene like the one that causes cystic fibrosis.

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designated DOCR1-917, or, more recently, simply 917, was found to be linked to the cystic fibrosis locus.[3] Linkage has also been shown for a site designated PON, the genetic determinant for serum activity of paraoxonase. Tight linkage was established between 917 and PON. The manner in which linkage analysis can be carried out in an individual family is shown in Figure 7. The family was informative because at least one parent heterozygous for cystic fibrosis was heterozygous for the two 917 alleles. In the father, the cystic fibrosis (CF) gene was on a chromosome containing the one allele. In this family there were no recombinations, but recombination was encountered with some frequency. So the linkage would not really be useful for prenatal diagnosis. The distance from the CF gene to 917 has been estimated at 15 centinograms and that from CF to PON at 10 centinograms.

Nevertheless, the identification of the RFLP marker locus was the breakthrough that made it possible to get much closer to the CF gene. The logic of the next step was to use the probe for the marker locus in a series of rodent-human hybrid cell lines that contained differing complements of human chromosomes to find the chromosomal location of the CF gene.[4] The 917 locus, and hence the CF gene, was found on chromosome 7. In fact, because one of the cell lines had a chromosome 7 with a partial deletion, it was possible to say that the site was on 7q.

Immediately it became possible to test for the linkage of the CF gene with other genes known to be located on the long arm of chromosome 7. Among the most useful was the *met* oncogene, which is located between 7q21 and q31 and displays mendelian polymorphism with two restriction endonucleases, *Taq*I and *Msp*I.[5] Linkage to the CF gene was found to be quite tight. No recombination was noted in 12 families studied in which at least one parent was heterozygous for the *met* locus. Similarly a tight linkage was also found between the CF gene and a locus that bound to an anonymous probe, pJ3.11, which defined an *Msp*I polymorphism that was mapped to the area of chromosome 7 between the centromere and q22.[6] The locus for the T-cell receptor β-chain, TCRβ, which maps to 7q3, proved to be on the same chromosome, but rather distant. The currently accepted lineup of the relevant genes on chromosome 7 is shown in Figure 8.[7] The gene for the collagen locus, COL1A2, is also at least 10 centinograms away from the CF locus.

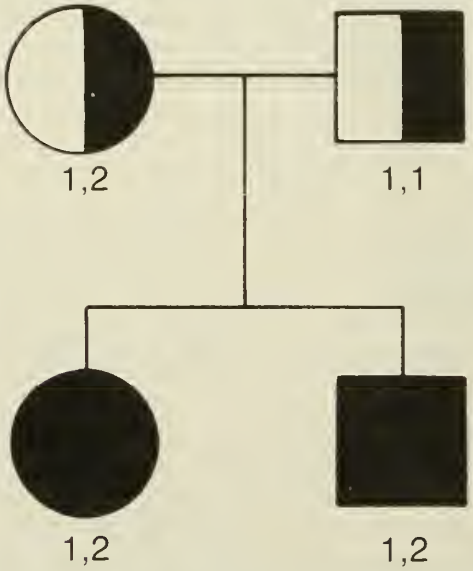

Figure 7.—The pedigree of a family with two children affected with cystic fibrosis (black symbols) is shown. The 917 alleles are designated 1 and 2 for the 6.3- and 5.3-kilobase fragments.

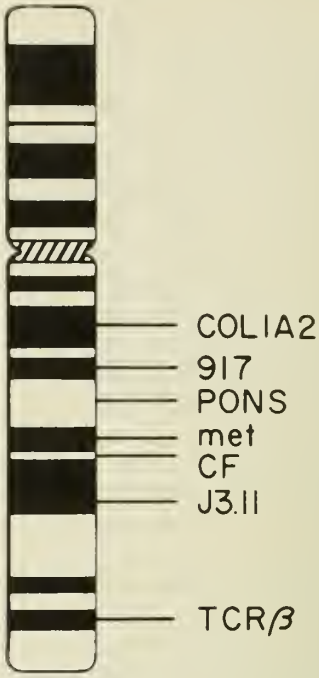

Figure 8.—A map of the human chromosome 7 shows the locations of the various probes and the cystic fibrosis (CF) gene. COL1A2 = the collagen gene, met = an oncogene, PONS = the serum paraoxonase gene, TCRβ = the T-cell receptor β-chain gene, J3.11 = an anonymous probe, 917 = a marker for a restriction fragment length polymorphism

These studies in the aggregate have shown clearly that cystic fibrosis is caused by alterations at a single recessive gene, which is responsible for the disease in all affected families. The linkage with J3.11 and *met* has permitted the launching of programs of heterozygote detection and prenatal diagnosis. At the same time, it has become evident that there is still enough distance between the markers and the CF gene itself that a substantial amount of further work will be required before the CF gene itself is isolated.

Additional linked markers are now available, including 7c22[8] and others.[9-16] Several heterozygotes have been identified using DNA markers. Approaches to prenatal diagnosis have combined the use of these markers with the analysis of amniotic fluid for intestinal enzyme activity.[8,17] The markers used have been *met*, J3.11 and 7c22. The DNA has been obtained by chorionic villus sampling and by amniocentesis and cell culture. In general, there has been diagnostic agreement between the results of the DNA markers and the intestinal enzyme data. A number of pregnancies have been predicted to be affected, and seven have been terminated.[10] Sweat tests available on eight infants confirmed the prenatal diagnoses of six of normality and two of cystic fibrosis.[10] A number of monitored pregnancies were continuing at the time of this report.[8]

These are exciting times in science. The rate of applying advances in fundamental molecular biology to the practice of clinical medicine is extraordinary. Nowhere is progress more abundantly evident than in cystic fibrosis.

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The Medical Uses of Hope

As I was eating breakfast one morning I overheard two oncologists discussing the papers they were to present that day at the national meeting of the American Society of Clinical Oncology. One was complaining bitterly.

"You know, Bob, I just don't understand it. We used the same drugs, the same dosage, the same schedule, and the same entry criteria. Yet I got a 22% response rate and you got 74%. That's unheard of for metastatic lung cancer. How do you do it?

"We're both using Etoposide, Platinol, Oncovin, and Hydroxyurea. You call yours EPOH. I tell my patients I'm giving them HOPE. Sure, I tell them this is experimental, and we go over the long list of side effects together. But I emphasize that we have a chance. As dismal as the statistics are for non-small cell, there are always a few percent who do really well."

"Aren't you giving them false hope with that approach? What do you do if they don't respond?"

"Alan," he said gently, "don't you give them false despair when you stress only the side effects of the treatment and the grimness of the prognosis? It's not ethical to minimize those. Neither is it fair to shut out the possibility of a good outcome. When patients have hope, they are more motivated, they withstand the chemotherapy better. When they look to the future, they may be afraid, but at least they have something to hold on to.

"Realistically, most will not survive the disease. I never promise cure. What I can offer, however, is my pledge not to abandon them. I can help patients switch their goals from cure to remission, from remission to control, and finally, from control to a death that is comfortable and as meaningful as possible."

My breakfast was over, and as I got up to leave, I thought, maybe I'll give my patients a little hope next time, too!

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Adrenocortical Function in the Acquired Immunodeficiency Syndrome (AIDS)

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs Homer A. Boushey, Professor of Medicine, and David G. Warnock, Associate Professor of Medicine, under the direction of Dr Lloyd H. Smith, Jr, Professor of Medicine and Associate Dean in the School of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, School of Medicine, San Francisco, CA 94143.

RICHARD K. ROOT, MD:* *Adrenal insufficiency has recently been recognized as a complication of the acquired immunodeficiency syndrome (AIDS), but recent work, much of it conducted by Ed Biglieri, MD, and colleagues at the General Clinical Research Center at San Francisco General Hospital and Medical Center, has revealed that less obvious abnormalities in adrenal function are common in patients with AIDS. He will review some of his findings with us today and will suggest ways of identifying patients requiring supplemental corticosteroid therapy over periods of stress or opportunistic infection.*

EDWARD G. BIGLIERI, MD:† Attention was called to the adrenal gland in patients with AIDS by a recent series of letters published in journals.[1-4] Adrenal insufficiency was documented in one instance before the clinical syndrome of AIDS. The human immunodeficiency virus (HIV) creates multiple defects in the immune system, increasing susceptibility to unusual infections and neoplasms. Many of the symptoms that occur in patients with AIDS, such as anorexia, nausea, vomiting, weight loss, fever, diarrhea, fatigue, and orthostatic dizziness, also occur in patients with acute adrenal insufficiency. Autopsy evidence of some degree of adrenal necrosis has been found in all patients dying of AIDS,[2,4-6] but the involved areas were small and focal, almost invariably affecting considerably less than 50% of the gland.[4,5] The clinical support for these pathologic findings was minimal, with only hyponatremia, hyperkalemia, hypotension, and few steroid values recorded, and the clinical diagnosis of adrenal insufficiency was often confirmed only by suboptimal cortisol responses to the administration of adrenocorticotropic hormone (ACTH; cosyntropin).

Because of this limited information, our group has evaluated adrenal function in patients with AIDS to determine the prevalence and the nature of adrenocortical abnormalities and to identify biochemical markers of early adrenal dysfunction.[7] We have carried out short-term and prolonged ACTH stimulation to identify and exaggerate the possible abnormalities.

The AIDS group consisted of 73 men and 1 woman, with a mean age of 36.7 ± 7.1 years. All the patients fulfilled the criteria of the Centers for Disease Control for the diagnosis of AIDS.[8] At the time of the study, none of the patients had hypertensive difficulties, clinical bleeding, or bacterial septicemia. None were receiving heparin, ketoconazole, phenytoin, or glucocorticoids. The tests were done at the end of their hospital stays for opportunistic disease or shortly after their conditions stabilized. In addition, we studied 19 male patients with the AIDS-related complex (ARC) who had a mean age of 36.4 ± 6.8 years. The ARC patients served as a chronically ill control group for the AIDS group. A group of 25 healthy persons with an age range of 19 to 24 years was also examined under similar conditions. Most of the patients were studied in the General Clinical Research Center at San Francisco General Hospital and Medical Center, with additional studies done at the Moffitt-Long Hospital at the University of California, San Francisco. Baseline morning specimens were taken after overnight recumbency for plasma cortisol, aldosterone, 18-hydroxycorticosterone (18-OHB), corticosterone (compound B), deoxycorticosterone, and 18-hydroxydeoxycorticosterone (18-OHDOC) levels. In all patients and normal subjects, ACTH 1 to 24 (cosyntropin, 0.25 mg) was administered intravenously in a bolus dose between 8 and 9 AM, and blood specimens were taken 60 minutes later for the same steroid levels. Prolonged superphysiologic stimulation by ACTH was achieved by giving 20 IU ACTH gel intramuscularly every eight hours for three days.

Adrenal Biosynthetic Pathways

Three major biosynthetic pathways in the adrenal gland were assessed (Figure 1). The zona glomerulosa, the outer zone of the adrenal cortex, produces aldosterone. Aldosterone and its immediate precursor, 18-OHB, are secreted into the peripheral circulation. The other steroids in this pathway are obligate intermediates in the biosynthesis of aldosterone and 18-OHB. The renin-angiotensin system is the principal regulator of this zone.

The zona fasciculata has two major pathways. The glucocorticoid or 17-hydroxysteroid pathway produces cortisol. The mineralocorticoid pathway or 17-deoxy pathway produces deoxycorticosterone, compound B, and 18-OHDOC. The zona fasciculata is regulated by ACTH. There are rare circumstances where there is a dissociation between the 17-deoxysteroids and the 17-hydroxysteroids during stimulatory or suppressive maneuvers.[9]

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(Biglieri EG: Adrenocortical function in the acquired immunodeficiency syndrome [AIDS] [Medical Staff Conference]. West J Med 1988 Jan; 148:70-73)

ABBREVIATIONS USED IN TEXT

ACTH = adrenocorticotropic hormone
AIDS = acquired immunodeficiency syndrome
ARC = AIDS-related complex
CRH = corticotropin-releasing hormone
HIV = human immunodeficiency virus
18-OHB = 18-hydroxycorticosterone
18-OHDOC = 18-hydroxydeoxycorticosterone
SD = standard deviation

Zona Fasciculata Steroid Levels and Responses to ACTH in AIDS

We found significant and unique abnormalities in adrenal function in a high proportion of AIDS patients (Table 1). Basal plasma cortisol levels are elevated when compared with those in unstressed normal subjects (433 ± 28 nmol per liter versus 298 ± 22 nmol per liter, $P < .001$). After short-term ACTH stimulation, however, the cortisol levels in AIDS patients were lower than in normal subjects (Table 1, Figure 2). Only 48% of AIDS patients had a 60-minute plasma cortisol level within 1 standard deviation (SD) of the mean value in normal subjects, but 86% were within the normal range (± 2 SD). In contrast to the plasma cortisol levels, the basal 17-deoxysteroid levels when compared with those in unstressed healthy subjects were normal, but after short-term ACTH stimulation, AIDS patients had significantly lower responses of compound B, deoxycorticosterone, and 18-OHDOC. Virtually all patients had reduced and stimulated 18-OHDOC levels. This limited stimulation of 18-OHDOC is an early indication of adrenal impairment. Three continuous days of superphysiologic levels of ACTH confirmed and amplified the impaired 17-deoxysteroid responses in the 14 patients who had subnormal responses to ACTH stimulation. Basal 8 AM plasma steroid levels were measured daily. Of the 14 patients, 10 achieved normal stimulated cortisol levels. The mean cortisol levels as a group were slightly lower than those in normal subjects ($P < .05$). The 17-deoxysteroid responses were uniformly subnormal (Figure 3).

The discrepancies between the two steroid pathways of the zona fasciculata were further assessed by measuring ACTH levels in 19 patients with AIDS; they were found to be normal in every instance (7.06 pmol per liter). Two patients who had normal cortisol but impaired 18-OHDOC responses to ACTH received an intravenous bolus injection of ovine corticotropin-releasing hormone (CRH, 0.1 μg per kg). In one

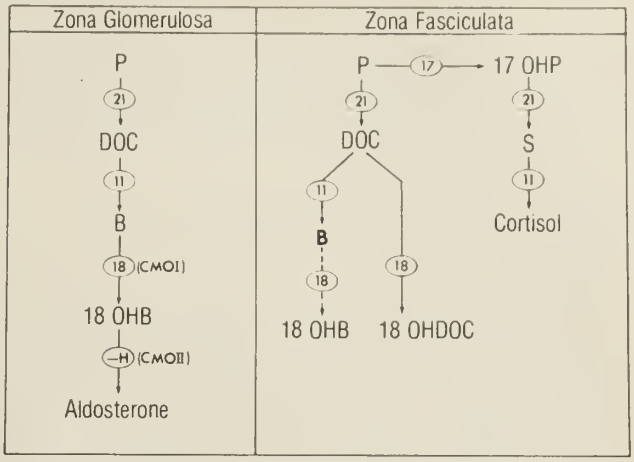

Figure 1.—The graph shows the three major biosynthetic pathways of the adrenal gland: the zona glomerulosa, which produces aldosterone, and the two major pathways of the zona fasciculata. B = compound B (corticosterone), CMO = corticosterone-methyl-oxidase, DOC = deoxycorticosterone, –H = dehydrogenase, 18-OHB = 18-hydroxycorticosterone, 18-OHDOC = 18-hydroxydeoxycorticosterone, 17-OHP = 17-α-hydroxyprogesterone, P = progesterone, S = 21-deoxycortisol, ◯ = hydroxylase action, ---- = only active with compound B excess

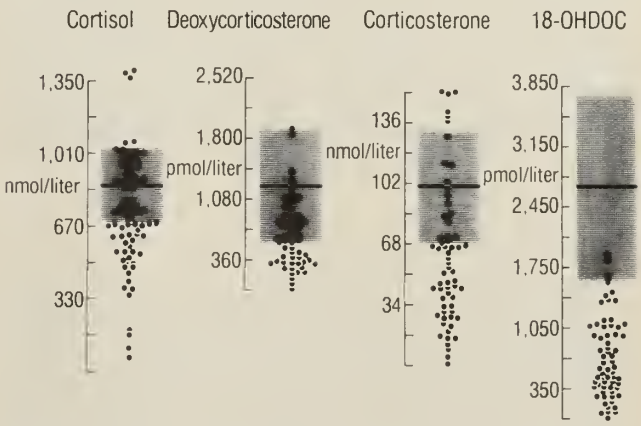

Figure 2.—The graphs show adrenocorticotropin (cosyntropin)-stimulated levels in patients with the acquired immunodeficiency syndrome (•) and in normal subjects (gray screen) for cortisol, deoxycorticosterone (DOC), corticosterone (compound B), and 18-hydroxydeoxycorticosterone (18-OHDOC). ▒ = mean ± 1 standard deviation in normal subjects

TABLE 1.—*Basal and Cosyntropin-Stimulated Values in Normal Control Subjects, Patients With AIDS-Related Complex (ARC), and Patients With AIDS*†*

	Normal Control Subjects (n=25)		*Patients With ARC (n=19)*		*Patients With AIDS (n=74)*	
Hormone	*Baseline*	*60 min*	*Baseline*	*60 min*	*Baseline*	*60 min*
Cortisol, nmol/liter	298 ± 22	855 ± 33	295 ± 25	618 ± 28‡	433 ± 28§	726 ± 30‖
DOC, pmol/liter	163 ± 15	1,235 ± 136	160 ± 21	599 ± 67‡	245 ± 24	723 ± 82§
Compound B, nmol/liter	8.9 ± 1.6	101.7 ± 6.6	10.6 ± 2.1	82.3 ± 6.1‖	12.4 ± 1.7	65.5 ± 6.1§
18-OHDOC, pmol/liter	150 ± 26	2,653 ± 222	152 ± 23	1,658 ± 130‡	115 ± 20	714 ± 58‡
18-OHB, pmol/liter	712 ± 66	3,887 ± 410	1,843 ± 1,012	3,860 ± 985	1,392 ± 245	2,872 ± 349
Aldosterone, pmol/liter	236 ± 25	829 ± 103	275 ± 86	613 ± 125	344 ± 69	533 ± 80

AIDS=acquired immunodeficiency syndrome, DOC=deoxycorticosterone, 18-OHB=18-hydroxycorticosterone, 18-OHDOC=18-hydroxydeoxycorticosterone

*The values represent the mean and standard error of the mean.
†Statistical differences are indicated between values in ARC and AIDS patients and comparable normal values.
‡$P < .001$.
§$P < .01$.
‖$P < .05$.

patient, plasma cortisol and 18-OHDOC levels responded in a manner similar to that caused by the exogenous ACTH test, but in the second patient receiving the same lot, neither the cortisol nor the 18-OHDOC level increased. These preliminary studies suggest there may be diverse pituitary defects associated with HIV infection.

Zona Fasciculata Steroid Levels and ACTH Responses in ARC

The basal plasma steroid levels in patients with ARC did not differ significantly from those in unstressed normal subjects (Table 1). The 19 patients with ARC, however, responded to ACTH stimulation subnormally, the mean responses being similar to those in patients with AIDS (Figure 4). Nine patients received ACTH for three days. Cortisol responses were normal, and 17-deoxysteroid levels did not differ significantly from those in normal subjects (Figure 3). By the third day of ACTH administration, cortisol levels in ARC and AIDS patients were not significantly different, but the 17-deoxysteroid levels were lower in AIDS patients.

Zona Glomerulosa Steroid Levels in ARC and AIDS

The zona glomerulosa function was assessed by measuring the basal levels of aldosterone and 18-OHB (Table 1). Plasma aldosterone, 18-OHB, and renin activity in the recumbent position and their responses to the upright posture in both ARC and AIDS patients were normal. Angiotensin III produced normal increases of both. Three days of ACTH stimulation produced normal patterns of aldosterone and 18-OHB. Aldosterone production appears normal in patients with AIDS and those with ARC.

Adrenal Insufficiency

Four patients represented by the lowest four individual values in Figure 2 had clinical adrenal insufficiency with ACTH-stimulated cortisol levels (< 138 nmol per liter), presumably due to HIV infection or opportunistic disease. Unexpectedly, ACTH levels were not elevated (< 20 pmol per liter) despite the reduced cortisol and aldosterone levels, hyperkalemia, and hypotension. In two patients, ACTH administration stimulated normal increases in cortisol but impaired 18-OHDOC responses before the appearance of overt clinical adrenal insufficiency.

Implications of Steroid Defects

The adrenal gland is the endocrine organ most commonly involved in AIDS, especially by cytomegalovirus, *Mycobacterium avium-intracellulare,* and other infecting organisms. The pathologic lesions are focal, mild, and of questionable clinical significance. Lipid depletion is a common finding and is noted in malnourished, chronically ill patients. Patients with AIDS are particularly susceptible to adrenal injury from hemorrhage and a variety of autoimmune phenomena including lupus erythematosus, autoimmune hemolytic disease, and autoimmune thrombocytopenia. The adrenal pathologic lesions described, however, are not sufficient to explain the usual steroid abnormalities seen in our studies. In addition, most of the reported adrenal lesions are in the adrenal medulla or zona reticularis. The zona glomerulosa and zona fasciculata appear to be spared.

Our studies show that the 17-deoxysteroids, in particular 18-OHDOC, have subnormal responses to short-term ACTH stimulation. The three-day ACTH study exaggerates and firmly establishes the impaired responses of these steroids in patients with AIDS. Patients with ARC, who we considered to be our chronically ill control group, also had reduced responses to exogenous ACTH, but, after prolonged stimulation, their cortisol and 17-deoxysteroid responses were normal. Again, the critical difference between the patients with ARC and those with AIDS was the greater impairment of the 17-deoxysteroids in AIDS. From these studies, we

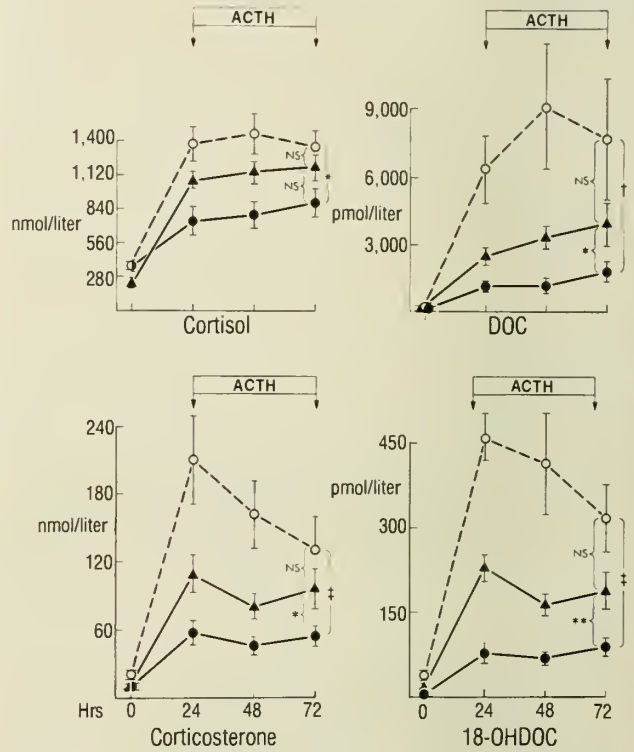

Figure 3.—The graphs show steroid levels during 72 hours of continuous adrenocorticotropic hormone (ACTH) stimulation. DOC = deoxycorticosterone, 18-OHDOC = 18-hydroxydeoxycorticosterone, NS = not significant, ○ = mean ± standard error of the mean (SEM) in normal subjects, ● = mean ± SEM in patients with the acquired immunodeficiency syndrome (AIDS), ▲ = mean ± SEM in patients with AIDS-related complex, * = $P < .05$, † = $P < .01$, ‡ = $P < .001$

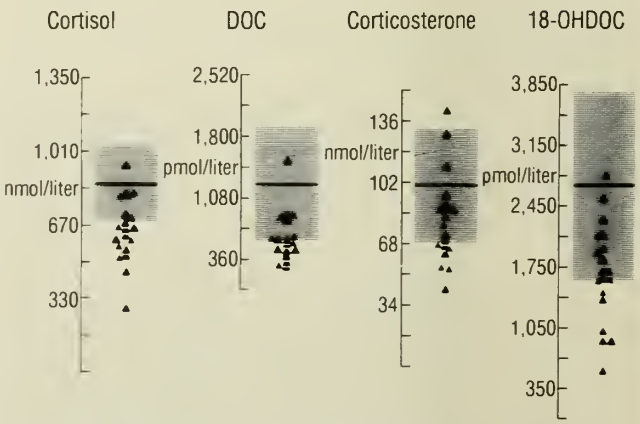

Figure 4.—The graphs show adrenocorticotropin (cosyntropin)-stimulated levels in patients with the acquired immunodeficiency syndrome-related complex (▲) and in normal subjects (gray screen) for cortisol, deoxycorticosterone (DOC), corticosterone (or compound B), and 18-hydroxydeoxycorticosterone (18-OHDOC). ▭ = mean ± 1 standard deviation in normal subjects

think it is important to identify those patients with early steroid defects and those with limited adrenal capacity. Failure to achieve a plasma cortisol level of 685 nmol per liter or greater after cosyntropin administration requires an additional three consecutive days of ACTH stimulation to determine the adrenal capacity. Those with cortisol levels of less than 994 nmol per liter (mean −1 SD in normal subjects) should be considered to have partial adrenal insufficiency and be treated with 100 to 200 mg of cortisol or its equivalent during acute infections or trauma. The simultaneous measurement of the 18-OHDOC level would be desirable but not essential in the management of AIDS, but these measurements would be of great value in patients with ARC or in high-risk groups because impaired stimulation by ACTH appears to be an early indicator of the neurotropic properties of HIV infection in the pituitary or central nervous system.[6] The ACTH stimulation test has its greatest value in identifying limited cortisol production in AIDS patients, whereas the 18-OHDOC levels are of greatest value in patients with ARC or in high-risk groups, which may identify those with an incipient adrenal abnormality.

The zona fasciculata appears to be one of the target zone tissues in AIDS. Early in AIDS, a dissociation exists between a normal cortisol response to ACTH and the response of the 17-deoxysteroids, which is impaired in virtually all patients. When signs and symptoms of adrenal insufficiency occur, plasma ACTH levels are not increased. In contrast to the events taking place in the zona fasciculata, the zona glomerulosa remains intact. This pattern of steroid production is commonly observed in cases of hypopituitarism, in which aldosterone production is normal and the zona fasciculata activity reduced. A pituitary defect is further confirmed by defective adrenal steroid responses to ovine CRH and the relatively small focal inflammatory, necrotic, or hemorrhagic lesions in the adrenal glands of AIDS patients. Our recent studies suggest that a non-ACTH extraadrenal factor regulates the 17-deoxysteroid pathway in the zona fasciculata.[9] A deficiency of this factor could be the initial defect. These observations do not exclude a primary adrenal lesion nor an early diversion of substrate steroids to cortisol in an ill patient, but the diversion in either case may be a consequence of a reduction of a 17-deoxy regulator. The possibility of a selective form of hypopituitarism also exists in AIDS. There may be two regulators of the zona fasciculata—one is specific for the 17-deoxy pathway, and the other (ACTH) regulates both the glucocorticoid responses and the 17-deoxy pathway (Figure 5). A reduction in the secretion of this non-ACTH regulator of the 17-deoxysteroids would lead to lower 18-OHDOC levels.

There is also evidence that the steroids of the 17-deoxy pathway can suppress some extraadrenal, non-ACTH, factor without affecting cortisol. Evidence comes from two observations, the first being an immediate postoperative evaluation. After the removal of a benign deoxycorticosterone-secreting tumor, the contralateral adrenal gland produces normal cortisol and 17-deoxysteroid levels and responds to ACTH with a normal increase in cortisol but not in the 17-deoxysteroid levels. ACTH responses are suppressed for as long as two months.[9] The second observation is that administering deoxycorticosterone acetate to normal subjects does not suppress cortisol but can suppress other steroids produced by the 17-deoxy pathway.[9] A unifying hypothesis could include a central nervous system (pituitary) infection with a reduction of zona fasciculata regulators, first the 17-deoxy regulator, then ACTH. Selective hypopituitarism and hypoadrenalism would result with later adrenal infection by opportunistic agents or HIV (infection) and adrenal insufficiency.

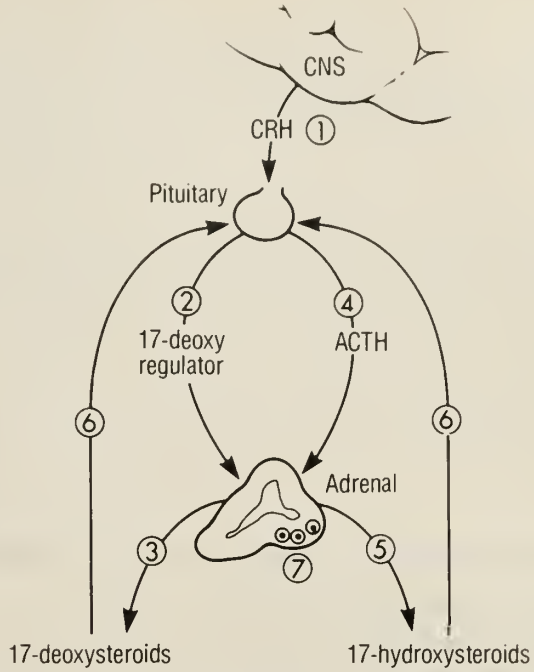

Figure 5.—A proposal for the mechanism of adrenal impairment in the acquired immunodeficiency syndrome is depicted, with the steps indicated as follows: ① a decrease in the corticotropin-releasing hormone (CRH); ② a decrease in the 17-deoxy regulator; ③ a decrease in the 17-deoxysteroids (deoxycorticosterone, compound B, and 18-hydroxydeoxycorticosterone); ④ a decrease in the adrenocorticotropic hormone (ACTH); ⑤ a limited cortisol production; ⑥ a reduced set of feedback of 17-deoxysteroids and 17-hydroxysteroids (11-deoxycortisol and cortisol) (pituitary); and ⑦ infection by an opportunistic organism. CNS = central nervous system

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Epitomes
Important Advances in Clinical Medicine

Occupational Medicine

The Scientific Board of the California Medical Association presents the following inventory of items of progress in occupational medicine. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome, and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, research workers, or scholars to stay abreast of these items of progress in occupational medicine that have recently achieved a substantial degree of authoritative acceptance, whether in their own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Occupational Medicine of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to Division of Scientific and Educational Activities,
California Medical Association, PO Box 7690, San Francisco, CA 94120-7690

Carpal Tunnel Syndrome—A Cumulative Trauma Disorder

REPEATED MECHANICAL STRESS can result in low-level injuries or "cumulative trauma," and there is increasing evidence that certain repetitive or forceful motions of the hands and wrists can contribute to the development of the carpal tunnel syndrome. Postulated mechanisms by which cumulative trauma might cause the disorder include one or more of the following: tendinitis, with attendant compression of the median nerve within the carpal tunnel; local ischemia; and injury to the myelin sheath or disruption of axonal flow, or both.

In epidemiologic studies of working populations, a number of mechanical risk factors for the development of the carpal tunnel syndrome have been proposed. A case-control study of the syndrome among production seamsters found an association with using a deviated wrist or pinching hand position, particularly during forceful exertion. In another case-control study examining aircraft assembly workers, the use of vibratory hand tools and, to a lesser degree, repetitive wrist motions were associated with the carpal tunnel syndrome. In a recent cross-sectional study of 652 industrial workers, the prevalence of the syndrome was examined in relation to the postural and force requirements observed for hand and wrist activities at each job. The disorder was clinically diagnosed more than 15 times more frequently among workers classified as having "high force-high repetitive" jobs than among those with "low force-low repetitive" jobs. A high degree of repetitiveness was found to be more strongly associated with the carpal tunnel syndrome than was a high degree of force. The carpal tunnel syndrome should be recognized as a possible cumulative trauma disorder when a patient's occupational or nonoccupational activities include repetitive or forceful hand-gripping or wrist-deviating motions or the use of vibrating tools.

There is evidence supporting the efficacy of surgical and nonsurgical therapy in the care of patients with the carpal tunnel syndrome. In cases due to work-related factors, however, no studies have evaluated whether surgical or nonsurgical therapy will better prevent recurrence if patients return to their previous occupations. For these reasons, when an occupational cause for the syndrome is considered, treatment should include the avoidance of repetitive hand stress and the use of wrist splinting and anti-inflammatory medications as a first line of therapy. The use of pyridoxine in the treatment of the carpal tunnel syndrome has been suggested, but there are little data regarding its efficacy in work-related cases. If conservative measures fail, surgical intervention should be considered.

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Expanding Awareness of the Hazards of Vinyl Chloride

VINYL CHLORIDE MONOMER is a gas that can be converted into polyvinyl chloride resin, which, with the addition of various stabilizers and plasticizers, may be converted into pellets, powders, pastes, or film, the sum of which will constitute 35% to 40% of plastic products made. Depending on the manufacturing process, the polyvinyl chloride resin will contain a varying proportion of residual vinyl chloride monomer that will vaporize subsequently, although this proportion has been greatly diminished during the past decade. If polyvinyl chloride burns, a small but consistent release of vinyl chloride occurs, although the major toxic combustion products are hydrochloric acid and carbon monoxide.

Vinyl chloride has long been known to be hepatotoxic and a central nervous system depressant. For more than two decades we have known that it causes the development of acroosteolysis or of Raynaud's phenomenon in certain exposed workers, and the identification of a characteristic vascular abnormality has explained the probable pathogenesis of these conditions. Vinyl chloride has also been reported to be the cause of "vinyl chloride disease," a syndrome resembling one or more of the collagen diseases, such as scleroderma, rheumatoid arthritis, systemic lupus erythematosus, or the mixed collagen syndrome.

The carcinogenicity of high doses of this gas in rats was first reported in 1970, and human exposure leading to an

unusual type of liver tumor—angiosarcoma—was reported in 1974. The accumulated reports of an increased risk of hepatic angiosarcoma associated with an antecedent exposure to vinyl chloride have achieved almost the same degree of acceptance in current medical wisdom as the association between mesothelioma and asbestos. Just as asbestos causes more cancers than mesothelioma, however, the carcinogenic activity of vinyl chloride is much broader than hepatic angiosarcoma. After absorption, it is metabolically converted to chloroethylene epoxide, which is highly reactive and binds covalently to nucleic acids, increasing the mutation rate in any tissue that can support this metabolic change. On this basis, it is not surprising that a 1981 review of the epidemiologic studies of workers exposed to vinyl chloride has shown a significant excess risk in four of eight studies of biliary and digestive system cancers, in five of eight studies of brain tumors, in three of eight studies of respiratory system cancers, and in one of five studies of lymphatic and hematopoietic system cancers. A more recent 27-year study of exposed workers in Norway reported only a single case of hepatic angiosarcoma but an increased risk of colon cancer, lung cancer, melanoma, and thyroid cancer.

The experimental and epidemiologic evidence for the carcinogenicity of vinyl chloride monomer is solid, but appropriate protective measures continue to be overlooked frequently. Because a large proportion of plastics manufacture takes place in plants too small to retain their own medical staff, it follows that many, if not most, cases of cancer associated with this gas will first come to the attention of nonoccupational-medicine physicians who need to be aware of the growing data base linking exposure to vinyl chloride and an expanding array of cancers. As was the case for asbestos, such medical recognition is likely to be essential to the achievement of effective exposure control.

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Recognizing the Health Hazards of Ethylene Oxide

ETHYLENE OXIDE (C_2H_4O) is an important industrial chemical used in sterilization and many manufacturing processes. At ambient temperatures, it is a gas. In vivo, it is rapidly distributed throughout the body. Short- and long-term exposures lead to respiratory tract irritation and may lead to central nervous system depression and seizures. At high concentrations, ethylene oxide can induce lethal mutations and cause embryotoxicity in rodents. It is able to alkylate DNA-causing gene mutations leading to sister chromatid-exchange abnormalities and chromosomal damage. Several types of tumors have been described in laboratory animals associated with ethylene oxide exposures.

Five longitudinal epidemiologic studies in occupationally exposed workers in Sweden, the United States, and West Germany strongly support the association of the agent with leukemia. The data cannot be considered conclusive, as the number of workers is relatively small and it is impossible to exclude completely exposure to other workplace carcinogens. Nevertheless, these epidemiologic studies strongly suggest that ethylene oxide is carcinogenic in humans. Studies of hospital workers with long-term ethylene oxide exposure, when compared with control populations with no significant difference in educational background, suggest that neurologic dysfunction may result from such exposure. These effects may occur at exposure levels that are common in hospital sterilizing procedures. The use of ethylene oxide is primarily limited to the sterilization of medical and food products.

Because the safe level of exposure to this agent is difficult to define, persons working in close proximity to hospital, laboratory, or food sterilizers should be informed as to the known and the uncertain risks. The function of sterilizing equipment should be regularly assessed to ensure there is no human exposure. The rationale for both environmental and medical surveillance needs to be presented to all potentially exposed persons.

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Carcinogenicity of Synthetic Mineral Fibers

SYNTHETIC MINERAL FIBERS such as fiberglass and mineral wools have assumed significant industrial importance and currently represent a $3 billion domestic industry. The durability, strength, and insulating properties of these fibers allow them to serve a wide variety of purposes, including insulation and structural support. Recognized health risks associated with synthetic mineral fibers include respiratory and skin irritation. They have been considered safe from the standpoint of cancer risk, making their use attractive in applications previously limited to asbestos fibers. Recent epidemiologic data suggest, however, that synthetic mineral fibers may be associated with increased lung cancer risk.

Concern over possible carcinogenic effects was raised in the early 1970s when it was shown that mesotheliomas could be caused in animals by instilling vitreous fibers into the pleural space. Fibers that were long, thin, and durable showed a carcinogenic potential equivalent to asbestos. Inhalation studies in animals, however, which probably represent a more appropriate model of human exposure, did not show these fibers to be carcinogenic or significantly fibrogenic.

Epidemiologic studies in human populations have also raised important questions regarding the health risks associated with synthetic mineral fibers. An increased prevalence of minimal interstitial changes has been found in chest radiographs of insulation plant workers exposed to these fibers. A large cooperative European study of more than 20,000 workers employed in the industry since the late 1930s showed an excess of lung cancers. Subjects whose first exposure occurred more than 20 years before the diagnosis of cancer and who began work in the early technologic phase of the industry's development were most strongly affected and had about a twofold increased lung cancer mortality. Similar results were reported among American workers in the industry. In comparison, lung cancer deaths among asbestos workers are increased fivefold in nonsmokers and 50-fold in smokers. Insufficient data are available to address the role of smoking

for patients with lung cancer associated with synthetic mineral fiber exposure. Malignant mesothelioma has not been linked to such exposure.

Excess lung cancers in these studies appear concentrated in groups that began working in the industry before protective measures, such as dust suppression, were widely introduced, which probably have significantly reduced exposure for contemporary workers. If the potential of these fibers to cause lung cancer is dose-related, as is the case for asbestos, then it is likely that less risk accrues to today's workers and that the danger to homeowners with attic insulation of synthetic mineral fiber is negligible. Measures to minimize exposure should be consistently and conscientiously applied, however, to avoid the tragic health and economic consequences associated with occupational exposures to asbestos.

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Preplacement Medical Examinations—Update

THE PREPLACEMENT MEDICAL EXAMINATION provides physicians with an opportunity to make an assessment of a job applicant's health risks through an examination of that person's past and present state of health. Federal regulations mandate that all employment medical recommendations be job-related. There has been a 10.5% increase in preplacement medical examinations throughout the country since 1975. Research examining their use has found that only 25% of the physicians who do these examinations have ever visited work sites to become familiar with the jobs. A large minority do not even refer to the job descriptions before making employment recommendations. A reluctance to address the "job-relatedness" of the medical evaluation places both the reliability and validity of these recommendations in question.

Although all decisions regarding employment recommendations require a thorough evaluation, making employment recommendations is extremely difficult when applicants have preexisting medical conditions that could affect their ability to safely do a job that is physically demanding. For these types of jobs, preplacement medical examinations are largely directed at detecting problems associated with the low back because those who have had one incidence of low-back pain are likely to have another. Additional studies have shown that a low cardiovascular fitness level is a risk factor for chronic back pain and can be detected during the examination.

If preplacement medical examinations are used as employment selection tools, they must conform to the federal regulations that mandate that employment selection procedures be based on job-related criteria. It is the burden of an employer to show that the medical standards used are indeed job-related. The burden this places on physicians is one of making an "informed" decision, which requires knowledge of specific tasks that will be required of a job applicant. This information is often synoptically presented in the job description and class specification, but the generality of these documents may be of limited value to a physician in making appropriate recommendations. The alternative is to evaluate an applicant using job-related information that has been collected through analyzing the most physically demanding or hazardous and essential tasks within a specific job. This information allows the physician to base the recommendation on an evaluation of the applicant's medical condition as it relates to the minimum physical abilities required to safely do the job.

An effective resolution of problems associated with the preplacement examination may require a comprehensive program consisting of strength and fitness testing and a medical examination developed on a job-related basis. Many public and private organizations currently meet these criteria. Though empirically unproved, these programs have a good potential for decreasing the incidence of job-related injuries and illnesses that may be caused by improper placements in various positions.

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What We Have Learned From Chernobyl

THE CHERNOBYL DISASTER of April 26, 1986, tested the ability of the Soviet medical system to provide emergency medical care in a civilian nuclear disaster of unprecedented scope. Within 12 hours, medical "brigades" composed of about 3,000 physicians and 2,400 nurses, paramedics, and laboratory technicians had been transported to the nuclear reactor village from as far away as Moscow (640 km [400 mi]) and beyond. The on-site medical emergency team was sorting out those firefighters who required hospital admission within 15 minutes of the explosion. By four hours, 108 of 204 of the firefighters were admitted to hospitals. By the end of two days, more than 350 victims of acute radiation sickness had been evaluated, medical charts assembled, and 1,000 leukocyte counts and differentials done to estimate radiation doses. Ultimately 203 seriously irradiated—> 199 rads—and thermally burned patients were admitted to hospitals in Moscow (129 patients) and Kiev (74 patients).

Despite state-of-the-art therapy that included bone marrow transplantation, 27 of 42 patients—19 patients with more than 600 rads total-body radiation dose and 23 patients with 400 to 600 rads total-body dose—died in hospital. (Two reactor operators died or were lost within six hours of the blast.) Of 171 patients with acute radiation sickness of less severity—dose estimates 100 to 400 rads—none died. All deaths were associated with severe thermal and β-radiation burns of the skin and upper respiratory system, injuries that are known from experiments in animals to enhance the lethality of otherwise tolerable radiation exposures. The rapid identification made under austere conditions of 203 among 24,000 persons exposed to clinically significant levels of total-body irradiation who required hospital admission and the

subsequent loss of only 29 of them are feats meriting our admiration of the Soviet physicians.

Representatives of the American Medical Association (AMA), various federal agencies, educational institutions, and the nuclear power industry have been meeting since the Chernobyl incident to increase the involvement of physicians in radiation emergency planning at the national and local level. The risk of radiation injuries involving transportation, spills in laboratories, clinics, hospitals, and other activities not directly related to nuclear power plants are now being evaluated by various groups, including the AMA's Advisory Committee on Nonmilitary Radiation Emergencies. Beginning in September 1987, the AMA, Oak Ridge (Tennessee) Associated Universities, and others have collaborated in demonstrating in numerous selected locations community physicians' preparedness for environmental mass casualty events.

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Psychogenic Illness in the Workplace

OCCURRING in a variety of populations, mass hysteria or epidemic psychogenic illness is a phenomenon noted to occur primarily where people have gathered for work or to attend school. The manifestations of this episodic form of illness have been defined as the occurrence in a group of people of a constellation of physical symptoms suggestive of an organic illness but resulting from a psychological cause, with each member of the group experiencing one or more of the symptoms. Mass hysteria is differentiated from physically caused epidemics by the absence of laboratory results and physical findings confirming an organic cause; the preponderance of illness in girls or women; the apparent transmission of illness by sight or sound, or both, or by word-of-mouth or the alleged detection of an odor; the presence of hyperventilation or syncope; a benign morbidity, frequently with an explosive or rapid spread or rapid resolution; relapses in the original site of an outbreak; and evidence of unusual physical or psychological stress.

In a study conducted in a Singapore electronics plant, a susceptibility to hysteria was greater among workers younger than 20 years of age and among those employees with less than three years of service. Among the workers affected were persons with histories of psychophysiologic difficulties, who appeared more dissatisfied with their work, and in whom there was evidence of comparable behavior at home.

Mass outbreaks have been witnessed among women employees claiming skin irritation from contact with mythical "paper mites" and carbon paper, and vaginitis has been reported among workers using long-neglected and unmaintained change facilities.

Every effort must be made to assure the absence of sources of toxic contamination by a thorough environmental evaluation and measurement. Physical examination of involved workers must be done as a rational basis for the reassurance given that there are no definable infections or allergic or toxic causes for the symptoms manifested. The predisposing factors of boredom, supervisory pressure to produce, physical stressors, poor labor-management relations, impaired interpersonal communication, and the lack of social support or networking should be identified and corrected to avert recurrences of the group malady. It is particularly important that the issue not be handled lightly and that managers, affected workers, co-workers, and the media be apprised of all pertinent findings and be assured that no "poisoning" is taking place.

In these days of the recognition of the "tight building" syndrome wherein agents released within structures may accumulate or the general ventilation may be inadequate, it is important that investigations be complete so that a diagnosis of epidemic psychogenic illness can be made with surety.

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Occupational Transmission of the Human Immunodeficiency Virus to Health Care Providers

THE RISK to health care providers from occupational exposure to the human immunodeficiency virus (HIV) is undergoing continued evaluation in several large prospective cohort studies in progress since 1983. To date, the cumulative results from these studies are reassuring. In more than 3,000 workers with frequent and intensive occupational contact with patients with the acquired immunodeficiency syndrome (AIDS) and with laboratory specimens, including more than 1,000 workers with needle-stick or other parenteral exposures to HIV, the rate of HIV infection is less than 0.1% and at least an order of magnitude less than the risk from a similar exposure to hepatitis B virus.

Despite the documentation of low titers of HIV in most body fluids, including saliva and tears, only blood has so far been implicated as a source of occupational HIV transmission. While parenteral needle-stick exposures account for most infections, 3 of the 11 documented cases of occupational transmission reported in the world's literature occurred during cutaneous contact with HIV, and one occurred after mucuous membrane exposure.

Health care providers and others who have occupational contact with blood or other body fluids should be instructed to use infection-control precautions to prevent direct contact with these substances. Because it is not possible to know with certainty which persons are infected with blood-borne pathogens, these precautions should be routinely applied by all providers and for all patients when contact is anticipated. The routine use of these precautions not only will reduce the risk of nosocomial transmission of HIV, but may also reduce the risk of transmitting or acquiring a variety of other pathogens commonly encountered in the health care setting.

Because the perceived risk of HIV infection frequently exceeds the known risk, educational and counseling services should be provided for all employees. In addition, resources and equipment for implementing infection control guidelines,

such as well-fitting gloves, masks, and protective eyewear, should be readily available. Consideration should also be given to monitoring the compliance with infection-control policies so that appropriate remedial interventions can be instituted. Supervisors should be responsible for assuring that employees are aware of the hazard and are complying with required work practices.

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Marijuana Testing

THE ANALYSIS of urine to detect drug use is widely used today to protect employee health and safety and to help maintain industrial quality and productivity. Marijuana testing procedures are of concern because the results are more difficult to interpret than results for other abused substances. Urine is currently the specimen of choice, being easier to test than either blood or saliva and, when testing positive, it will remain so for a longer period of time. Urine testing is less invasive, less costly, and has a shorter turnaround time than blood testing.

Marijuana (Δ9-tetrahydrocannabinol [THC]) enters the circulation rapidly by smoking (minutes) and more slowly by ingestion (1½ to 3 hours) and is so highly metabolized that only a small fraction that enters the bloodstream is excreted unchanged in the urine. THC is rapidly converted by hepatic enzymes to several metabolites, the most prevalent of which is THC carboxylic acid. THC is stored mostly in adipose tissue and may accumulate faster than it can be removed in persistent users. For example, in a person using three or more joints per day who stops smoking marijuana completely and then adopts an exercise fitness program, thereby mobilizing body fat, urine specimens will test positive for THC at 50 ng per ml to 100 ng per ml or more for over two months, whereas one who smokes an occasional joint will test positive at from 50 to 100 ng per ml or more for three to four days. In addition, passive inhalation of marijuana smoke by nonusers occasionally will result in a concentration of 20 ng per ml and in rare cases as high as 40 ng per ml. THC testing is divided into sensitive screening tests (presumptive) and specific confirmatory tests (definitive). Most current screening technology involves immunoassay techniques, the private sector using primarily the enzyme-multiplied-immunoassay technique—EMIT-d.a.u. for a large number of specimens (more accurate), and EMIT-st for a small number of specimens (less accurate) (Syva Corporation)—whereas the federal government and military prefer the radioimmunoassay (RIA, Roche). A fluorescent immunoassay technique using polarized light—known as TDx (Abbott Laboratories)—has recently become available.

Abnormal immunoassay results do not necessarily imply the presence of THC, as any other agent in the specimen that binds to the antibody will result in a false-positive test. Also, the EMIT screen may test false-negative if a specimen is adulterated by the addition of bleach, detergent, salt, or vinegar or diluted with water from a tap or a toilet bowl.

Gas chromatography/mass spectrometry (GC/MS) is currently the most reliable confirmatory technique. In terms of analytic accuracy, EMIT-d.a.u. has a specificity in the range of 90% and a sensitivity in the range of 95%. GC/MS has a specificity of greater than 99.9% and a sensitivity of greater than 99.9%. Thus, a combination of screening by EMIT and confirmation by GC/MS will yield virtually 100% accuracy in testing for marijuana.

Marijuana testing as part of a well-designed program for the screening of employees and applicants for substances of abuse may help define the magnitude and seriousness of the problem and protect and improve health and safety in an ethically acceptable manner.

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Occupational Health Implications of a Toxic Spill of Propylene Dichloride

GIVEN THE ENORMOUS VOLUME of potentially hazardous materials being transported, it is inevitable that clinicians will see patients who have been exposed as a result of accidental spills.

On February 5, 1981, a truck containing propylene dichloride leaked 2,000 gallons. Propylene dichloride is a volatile chlorinated hydrocarbon that is a mucous membrane irritant and a central nervous system depressant. As a result, hundreds of people were evacuated from their homes; 129 persons were treated at a nearby emergency department, 15 of these being admitted to hospital. The persons exposed included truck drivers who were also present at the site of the spill, 2 California Highway Patrol officers, 12 firefighters, and a number of hospital employees who were secondarily exposed as a result of contact with the victims' contaminated clothing. A number of those persons had persistent complaints.

Propylene dichloride and closely related materials have been used as soil fumigants for a number of years. Unfortunately, there have been previous incidents involving the accidental release of propylene dichloride or related materials in combination with other agents. Some of those exposed experienced a good deal of chest discomfort, dyspnea, and cough; of this group, some had persistent chest pain or discomfort and fatigue.

Physicians involved in treating workers exposed to such an accident or release face many challenges. A step-by-step approach for the management of these types of exposures has been outlined. Indeed, the emergency department experience of persons in the above-cited accident reinforces the need for advance planning for both examination and treatment. The treatment of patients who have inhaled irritant materials in general focuses on supportive management. This includes the use of oxygen, bronchodilators where important, and, in the view of some authors, the use of systemic steroids to minimize complications.

Hospitals are rarely well prepared to minimize exposure of their own personnel to chemical hazards. The hospital spokesperson in this circumstance indicated that the emergency room personnel wore caps and gowns. Surgical masks will be of minimal, if any, benefit in dealing with possible chemical inhalations. Hospitals might be well advised to have available in their emergency departments a number of respirators designed to protect against exposure to organic vapors. Personnel need to be trained in the use of respiratory protection.

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Reactive Airways Disease Syndrome

THE REACTIVE airways disease syndrome describes the development of airway hyperreactivity and asthmatic symptoms following a single exposure to a high level of pulmonary irritants. The syndrome differs from occupational asthma in several ways: First, it develops only with very high levels of exposure to materials that are directly irritating, whereas occupational asthma develops after repeated exposures to relatively low levels of sensitizing materials. Second, the reactive airways disease syndrome develops after only a single exposure, whereas occupational asthma depends on repeated exposures with sensitization. Third, while patients with occupational asthma have a particular sensitivity to the material causing the syndrome, such as toluene diisocyanate, patients with reactive airways disease are not peculiarly sensitive to the causative agent. Fourth, a large fraction of occupational asthma is caused by allergic sensitization, whereas this is not the case with the reactive airways disease syndrome.

The diagnosis of the syndrome is based on two factors: first, a history of exposure to a high level of a toxic material, and, second, the presence of airway hyperreactivity. Various toxic, nonsensitizing materials have been shown to cause reactive airways disease, such as sulfur dioxide and ammonia. In addition, we have observed its occurrence due to bromine and to products of plastic pyrolysis (burning plastic).

Airway hyperreactivity may produce intermittent dyspnea and wheezing. Although spirometry findings may be normal between exacerbations, airway hyperreactivity can be detected and objectively quantified by tests of airway hyperresponsiveness. Airway function is determined by spirometry (or whole-body plethysmography) as a baseline and after administering a placebo, such as a saline aerosol. Gradually increasing doses of the provocative agent are then inhaled, with airway function measured after each dose. An abnormal response—such as a 20% decline in the forced expiratory volume in one second—will not occur in normal persons. The test is safe to do because it is discontinued after the first abnormal response to the increasing doses; if necessary, an inhaled bronchodilator may be used to reverse the bronchospasm.

Symptoms developing after a heavy exposure in a previously asymptomatic patient suggest reactive airways disease. Treatment should be similar to that for asthma. Workers with the syndrome can have asthmalike symptoms and physiologic impairment years after the incident. The long-term prognosis is uncertain.

Reactive airways disease is specific for high-level exposures; low-level exposure to respiratory irritants has not been shown to produce the syndrome. In summary, the reactive airways disease syndrome is a new name for an old phenomenon. Despite improved industrial hygiene practices, accidental single episodes of high-level exposure unfortunately are still frequent. Physicians should counsel patients after such exposures to report any symptoms suggestive of asthma or respiratory impairment so that appropriate confirmatory testing may be done. In addition, clinicians should carefully question patients with adult-onset asthma about any acute exposure events surrounding the onset of their asthma.

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Passive Smoking and Lung Cancer

ACTIVE CIGARETTE SMOKING has been amply shown to be the major cause of lung cancer. A dose-response relationship is seen with no apparent threshold, consistent with current biologic theory. Side-stream smoke, the smoke released from a burning cigarette tip, contains all the toxic and carcinogenic compounds in mainstream smoke, many of which are found in significantly higher concentrations in side-stream than in mainstream smoke. Studies of nonsmokers have shown that exposure to environmental tobacco smoke results in the uptake of tobacco smoke constituents. Thus, one would predict an increased lung cancer risk from such exposure.

Recent epidemiologic studies have now consistently shown an increased risk of lung cancer among nonsmokers exposed to environmental tobacco smoke. At least 13 studies from 6 countries have been reported, 11 of which found an increased risk of lung cancer among nonsmokers. The magnitude of the risk for the highest exposed groups has generally been in the range of twofold to threefold, but small sample sizes resulted in wide confidence limits for many of the estimates. The data on passive smoking have been reviewed in the Surgeon General's report, which found that "Involuntary smoking is a cause of disease, including lung cancer, in healthy nonsmokers." A recent review by the National Academy of Science also found that "exposure to [environmental tobacco smoke] increases the incidence of lung cancer in nonsmokers." For both of these reports the epidemiologic studies were critically reviewed and the conclusion made that errors in these studies did not negate the observed findings. The average increase in the lung cancer risk for nonsmokers exposed to environmental tobacco smoke is generally felt to be about 30% above the risk for nonsmokers without such exposure, or a relative risk of 1.3. This estimate is consistent with estimates based on low-dose extrapolation of active smoking risk models.

Many of the epidemiologic studies have considered only spousal smoking or home exposure as the source of environ-

mental tobacco smoke, but some more recent studies have considered such exposure at work and have found that the workplace may be a significant source of exposure. For example, a study based on data from the Los Angeles County Tumor Registry found that workplace exposure to environmental tobacco smoke additionally increased the lung cancer risk observed from spousal smoking alone. This finding is not surprising, as some estimates are that exposure to environmental tobacco smoke in the workplace may, on an average, be four times that at home. In general, such exposures have been poorly estimated for the workplace, and further work is necessary in quantifying this important source of exposure.

In the 1980s we have seen increasing regulation of smoking in the workplace. Smoking has been banned in 35% to 40% of private businesses and in many government offices. Interestingly, actions to ban or regulate smoking in the workplace are supported by a large majority of both smokers and nonsmokers. As the trend to cleaner air at work continues, physicians (and companies) may see more reductions in smoking rates, with associated decreases in the health costs from active and passive smoking.

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Agricultural Health Hazards

EDITOR'S NOTE: The following mini-review is also sponsored by the Advisory Panel to the Section on Occupational Medicine.

AGRICULTURAL WORK is demanding. Because the work is done outdoors and is invigorating, physicians may be unaware that agriculture has many health risks. The following occupations are included in this industrial group: farmers and farm managers; field workers or farmworkers (seasonal or permanent); pesticide mixers, loaders, and applicators; and greenhouse/nursery workers. In this review I will focus on the agricultural exposures that are linked with respiratory disease (farmer's lung), cancer of different sites, dermatitis, and accidental mortality.

Patients with farmer's lung present with allergic alveolitis usually after exposure to moldy hay or grain. The hay contains thermophilic microorganisms such as *Micropolyspora faeni* and *Thermoactinomyces vulgaris.* Inhaling the spores usually produces an acute bronchoconstriction that may include bilateral crackles, a positive antibody test for the suspected antigen, and reduced lung volumes and diffusing capacity. Prolonged exposure can produce a slowly progressive pulmonary fibrosis. Allergic alveolitis may also arise among agricultural workers involved with mushroom cultivation, barley malt production, cheese making, poultry handling and breeding, and fur processing. The Surgeon General reports that nonsmoking grain workers have about five times the prevalence of chronic bronchitis compared with nonsmoking controls; among grain workers who smoke, there is ten times the risk of bronchitis compared with nonsmoking controls.

Farmers and farmworkers smoke a third to a quarter less than all workers in the United States and generally have lower than expected risks for cardiovascular and cancer mortality. In particular, cancer sites related to cigarette smoking—that is, lung, kidney and bladder, and esophagus and larynx—show a consistently lower risk when compared with the general population. There appears, however, to be an association between farming occupations and cancers of the brain, prostate gland, skin, soft tissues, and the lymphatic and hematopoietic systems, including leukemia, Hodgkin's disease, lymphoma, and multiple myeloma. Explanations for the causes of brain and prostate cancer excesses are unclear. Nonmelanoma skin cancers, including cancer of the lip, are caused by a high exposure to ultraviolet light. The lymphatic cancers (and soft tissue sarcomas) among agricultural workers may be linked to exposure to chlorophenols and phenoxyacetic acid herbicides (that were contaminated with detectable levels of dioxin). In particular, in a 1986 study, non-Hodgkin's lymphoma (but not soft tissue sarcomas or Hodgkin's disease) had a sixfold odds ratio among Kansas wheat farmers exposed to 2,4-dichlorophenoxyacetic acid (2,4-D). The risk rose with the number of days exposed per year and was greater among those who mixed or applied herbicides directly. Pesticide applicators appear to have a slight lung cancer risk, but more studies are needed on this group of workers, especially those who have applied 2,4-D extensively.

Occupational dermatitis is highly correlated with the agricultural use of pesticides among farmworkers and among licensed mixers, loaders, and applicators. In California, a third to half of all cases of pesticide poisonings reported by physicians result in dermatoses, and there is a striking frequency of dermatitis among table grape workers compared with other agricultural crops. This result is not surprising given the high foliar contact and careful handling required in the harvesting of table grapes. The top three pesticides cited in California pesticide illness reports are propargite (Omite), elemental sulfur, and glyphosate (Roundup). There was a recent outbreak of chemical dermatitis affecting the necks and chests of 114 citrus workers from Tulare County, California, exposed to Omite-CR, a timed-release organosulfite miticide manufactured by Uniroyal. In addition to pesticide exposure, dermatitis may be related to crop contact, heat, preexisting atopic status, the presence of irritating weeds, or other factors. Organophosphate pesticide exposure can depress erythrocyte or plasma cholinesterase levels and can impair normal neurobehavioral function. Dibromochloropropane produces azoospermia among pesticide formulators.

The standardized mortality ratios (SMRs) of agricultural workers (farm supervisors, farmworkers, and nursery workers) aged 16 to 64 years who died between 1979 and 1981 were presented in the California Occupational Mortality study. The overall SMRs for white and black male agriculture workers was 166 and 250, respectively, both statistically significant. The causes of death contributing most to the overall risk among whites were falls and machinery accidents (SMR 380) and other accidents (SMR 310). Among black male agricultural workers, a similar SMR of 250 was reported for other accidents. These findings strongly suggest the need for improved safety designs for agricultural equipment and educational and interventional programs targeted at young male farm workers to lower the risks of accidental mortality.

In sum, new research and preventive programs are needed on cancer and pulmonary disease risks. Respiratory disease hazards are borne out by the significant risks for chronic obstructive pulmonary disease mortality among white and black male agricultural workers in the California Occupational Mortality Study report, with SMRs equaling 147 and 256, respectively. The occupational mortality study also reported that cirrhosis and other liver disease mortality was significantly elevated for white and black farmworkers (SMRs are 221 and 482, respectively), and the possible correlation with pesticide exposure should be examined. Pesticide exposures can be reduced by using integrated pest management methods, but given the current use patterns and regulatory climate, physicians will likely continue to see outbreaks of dermal and systemic poisonings such as the Omite-CR epidemic. New epidemiologic research combined with accident prevention programs is needed to preserve the health of agricultural workers.

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Editorials

Musings on Whither Medical Education

THERE IS A GROWING FEELING that something is wrong with medical education. Perhaps it has ever been thus, but now the complaints seem more strident and more frequent. Some think the time of education too long, others, too short. There are those who think it teaches too much basic science, replaces ideals with cynicism, or destroys good attitudes. Quite a few think it produces too many physicians who are more interested in impersonal science than in the more personal aspects of caring for patients. Yet withal, the system has produced good doctors, certainly the world's best trained doctors, but an uncomfortable feeling persists that they may not be all that well trained for what they are really expected to do. There is an unsettling sense that too many of them have much, perhaps too much, to learn about the real world of patient care after they have finished their formal training and find themselves out in practice.

Medical educators seem somehow loath to change anything very much. For many, their principal interest and hands-on experience is with modern medical science, and the educational system they dominate seems to have been designed to teach as much of this science as possible. Yet maybe it is time to ask to what extent the practice of medicine or health care is really hard science, or science at all, or put another way, just how much bioscience does one need to know to practice good medicine? Are there other experiences and skills that are important, perhaps even just as important?

There is good reason to believe that a new and different emphasis in health care is beginning to add some quite new dimensions to the traditional diagnosis and treatment of the sick. For example, more attention is being given to health and being well and to the prevention of illnesses and injuries that result from such things as aberrant human behavior, unhealthy lifestyles, economic or cultural deprivation, or an unhealthy working or living environment. This is relatively new in patient care and is clearly adding new dimensions to medical practice and health care. Are these new dimensions not, or should they not, also be essentials for an adequate medical education? And could it be that this lack in most physicians' interest and training is one reason why vacuums are beginning to appear in what one might expect to be the scope of medical practice, vacuums that are beginning to be filled by other health professionals who may not have the expertise that is really needed: the scientific and experiential expertise of physicians?

If there is any truth to all of this, it is hard for a thoughtful person not to believe that something is wrong with medical education. If so, there is much at stake for the future of the medical profession. Some might even suggest that medical education seems to be traveling down a dead-end street, heading for some kind of a cul-de-sac of bioscience, while forgetting that the main road of medical education should lead in the direction of producing physicians trained to meet the evolving needs of today's patients and today's society.

Change, if there is to be any, must come either from within or without. There will need to be pressures from somewhere. Will those pressures come from the medical profession, the medical educators, or the government? Actually, each has recognized a need and has tried to bring about some change. The American Medical Association and the Association of American Medical Colleges have both conducted formal studies and made formal recommendations, but so far, little significant change has resulted. A few of the specialty boards have begun to add new requirements that will bring more human dimensions to graduate medical education in those specialties. One or two medical schools are instituting substantive curricular changes that attempt new and more realistic approaches to teaching and learning that may begin to address new professional and societal needs. One can hope that some will prove to be useful as models. But perhaps the most effective change agents to date have been the government initiatives that promote the education and training of much-needed primary care specialists, that train physicians and other health professionals to practice in the still medically underserved areas and with underserved groups, especially minorities. Other actions by government have begun to reduce the funding available for the graduate training of specialists and subspecialists who are no longer needed in the same numbers and may even be adding disproportionately to the cost of health care.

Again, there is much at stake in all this for the future of the medical profession and health care in this nation. Events in the real world are moving rapidly. Much more needs to be done to educate and train young physicians in the right numbers and with the right preparation to understand and to effectively do what is rightly expected of them in medical practice and health care, not just in the coming decade but well into the next century. The lead time for doing what needs to be done in medical education is uncomfortably short.

MSMW

Cystic Fibrosis—On the Threshold of a Rational Therapy

THREE EVENTS DURING the past 50 years mark the major advances in our understanding of cystic fibrosis, a relatively common genetic disorder with protean manifestations and, even today, a rather grim prognosis. The first of these involved a detailed pathologic[1,2] and clinical[2,3] description of cystic fibrosis that permitted separation of this group of patients from others with similar signs and symptoms. These reports and the extensive descriptive clinical literature that appeared in the next two to three decades were substantially augmented by the second of these major events—that is, recognition of an abnormality in sweat electrolyte content[4] and the design of a convenient, safe, inexpensive, and reliable method for the measurement of sweat electrolytes.[5] Improved case detection, early therapy, reliable epidemiologic studies, and a focus of a considerable amount of research on water and electrolyte transport mechanisms in normal persons and patients with cystic fibrosis resulted from the development and wide use of sweat tests in clinical practice. The third event began two years ago and continues. That is, the "CF gene" has been localized to a region on the long arm of chromosome 7,[6-10] and the suggestion was made in a recent publication that the gene itself may have been located precisely.[11]

The first case described in the Specialty Conference elsewhere in this issue of the journal and the discussion by Drs Harwood, Edwards, and Nyhan illustrate the impact of these

landmark events. The child had intrauterine and early postnatal signs of the multisystem manifestations of cystic fibrosis. Meconium ileus, meconium peritonitis, diarrhea, and a failure to gain weight are manifestations of pancreatic insufficiency. His recurrent respiratory problems, requiring two additional admissions to hospital, were typical of the effects of the chronic intermittent inflammatory disease of airways in patients with cystic fibrosis. The disease was definitely diagnosed at age 2 months by the finding of an elevated chloride concentration in sweat in the context of these symptoms. Although nutritional problems were prominent in this patient's course, it is clear that the most important cause of morbidity and mortality—accounting for more than 95% of all deaths due to cystic fibrosis—is related to the respiratory system. Chronic bronchitis and bronchiolitis with intermittent involvement of lung parenchyma, colonization with a mucoid form of *Pseudomonas aeruginosa*, and the functional consequences of progressive destruction of the pulmonary architecture ultimately lead to cardiopulmonary failure.

In spite of advances in therapy and the promise of some recent approaches to the management of the pulmonary disease, such as aerosolized antibiotics, systemic anti-inflammatory agents, vaccines, and the like, the prospect for definitive treatment of this aspect of cystic fibrosis remains uncertain. Nevertheless, substantial developments in the use of noninvasive diagnostic methods, alluded to by Dr Edwards, and improved treatment of the complications of chronic obstructive pulmonary disease will be of benefit. Perhaps the Western Consortium CF Database referred to by Dr Harwood will assist in the evaluation of new and "established" approaches to therapy while fundamental studies directed toward basic mechanisms are in progress. The collection and storage of and access to medical data require attention not only in the case of patients with cystic fibrosis but for patients with any complex condition requiring input from many specialists in diverse disciplines. We should not underestimate, however, the formidable problems involved in generating even a limited patient data bank. The National Cystic Fibrosis Foundation, after more than five years of effort in that direction, has only recently put a modest system in place.

The truly remarkable progress of the past two years, summarized in Dr Nyhan's remarks, deserves some consideration inasmuch as opinions will be solicited among physicians outside the fields of genetics, pulmonary medicine, and other specialties relevant to the care of patients with cystic fibrosis and clinical research in this patient population. Moreover, the questions are similar to those raised in the context of other genetic disorders and even acquired diseases, such as the acquired immunodeficiency syndrome. It is certain that pressure will be generated for screening programs to detect heterozygous carriers of the mutant gene in large populations, for the antenatal diagnosis of cystic fibrosis, and application of the findings for abortion of an affected fetus. Clearly such programs and decisions raise many complex issues, only a fraction of which have been addressed by the medical and scientific community.

Technical concerns about the application of linked genetic markers and the provision of adequate counseling services by persons competent to evaluate the genetic data are but two of these questions already explored by investigators and clinicians. Considerable time and effort have been given to ensuring quality control, but other questions have been less widely discussed. For example, should large populations be screened for the cystic fibrosis gene defect? What will the consequences be for those persons identified as carriers of the gene? What of their offspring? Will medical and life insurance be available to them? What job opportunities will be denied to them? Who will pay the costs of screening? Finally, will elective abortion of an affected fetus be justified if the median survival of patients with cystic fibrosis increases to 40 or 50 years rather than 21 years, as it is today? Many of these questions involve personal choices, but others are matters of public policy about which physicians will be consulted.

In any event, the most important effect of the application of this work to the problem of cystic fibrosis will be a definition of the molecular basis of the disease. Recent studies have identified a defect in epithelial ion transport that is demonstrable in vivo and in tissue culture. Several investigations suggest abnormal chloride transport in sweat ducts and airway epithelium that, based on the data from Frizzell and co-workers[12] and Welsh and Liedtke,[13] could result from either a defect in the ion channel, a defect in a regulator of the channel, or a specific inhibitor of the channel in the cystic fibrosis cells. Both laboratories have studied chloride channels using patch clamp techniques. This method allowed analysis of single channels in situ and in excised patches. These β-adrenergic gated chloride channels are defective in the cystic fibrosis cell but active in the excised patches, suggesting a defect in channel regulation as the most likely of the possible mechanisms.

In the late 1940s the median survival for patients with cystic fibrosis was less than 1 year of age. By the mid-1970s the prognosis for patients with cystic fibrosis improved to about what it is today: a median survival of almost 20 years. That is, over the past decade, little progress has been made in the treatment of this disorder. Recent work in R. Williamson's laboratory[11] suggests that a candidate for the "CF gene" has been isolated. Further work to test this hypothesis is in progress and definitive data on this point will soon be in hand. Identification of the gene product and the defect responsible for cystic fibrosis will likely either affect therapy directly or focus efforts toward a more rational approach to the management of patients with cystic fibrosis. One can safely predict that this will have a major impact on the morbidity and mortality due to this disease.

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AIDS, Cancer, and Snakebite—What Do These Three Have in Common?

AN ESTIMATED 1 million persons throughout the world are bitten each year by venomous snakes; the number of deaths must approach 100,000. In the United States, approximately 45,000 people are bitten by various venomous and nonvenomous snakes annually, while about 8,000 of these are bitten by poisonous snakes native to our country. Venomous snakes are found in every contiguous state except Maine, while bites by these reptiles are most common in Texas, Florida, the Carolinas, Georgia, Mississippi, Louisiana, Arkansas, Oklahoma, Arizona, and California. Obviously, the incidence of snake venom poisoning is highest where humans and snakes overlap or cohabitate, although the actual number of snakes may be far higher in some more remote areas of our country.

About 70% of all bites by venomous snakes in the United States are inflicted by rattlesnakes (genera *Crotalus* and *Sistrurus*), 20% by copperheads *(Agkistrodon contortrix)*, 9% by water moccasins or cottonmouths *(Agkistrodon piscivorus)*, and less than 1% by coral snakes *(Micrurus* and *Micruroides)*. The incidence of bites by exotic (non-US) snakes is on the increase and is highest in New York, Boston, Miami, Los Angeles, and San Diego. Approximately 30 such cases are known for 1984.

As can be expected with such a highly variable type of poisoning, it is difficult to recommend a single therapeutic protocol for snakebite, not only because of the differences in the toxicity of the venoms of the different species, but because of the differences in the amount of venom a snake may inject. For example, in my experience with more than 900 cases of snake venom poisoning, and with respect to the rattlesnakes, 24% of the bites did not involve envenomation—that is, they were dry bites. In about 50% of the elapid (cobra, krait, and coral) bites seen by me, there was no poisoning, and statistics for sea snake and true viper bites also indicate, among other things, that there is a wide variation in snake venom poisoning. This obviously gives rise to all manner of folk and native cures, many of which, like the most recent suggestion of electroshock, find their way into the medical literature.

The basic therapeutic approach throughout the world during the past 50 years has been the use of antivenin. It has been said that antivenins have saved 75% of the lives that would have been lost had we not had recourse to this antitoxin, and there is no question that morbidity, worldwide, has been greatly reduced and hospital time and medical costs cut drastically through the use of this agent.

The use of antivenin has had its problems, however. Some of the early antivenins (1906-1930) more often than not precipitated serious reactions, which in those days sometimes ended in death. Today's antivenins can be considered both effective and safe, although they could be improved upon. Only one death in the United States during the past 35 years has been attributed to anaphylactic shock precipitated by the antivenin used for rattlesnake bites. This record can be equaled by few other drugs. The contention that antivenins are dangerous because of the high number of delayed serum reactions following the use of horse-host antivenins is not warranted and is indeed poor advice, in view of the simplicity of the reactions and the availability of effective follow-up care.

The major question when using any antivenin is "How much?" This is not easy to answer, as it depends primarily on the degree of envenomation, which in some cases may be difficult to determine. The various ad hoc committees on snakebite of the World Health Organization have wrestled with administration times and doses for more than 20 years. One conclusion has become obvious. In the 1950s and 1960s, all of us used far too little antivenin in terms of individual cases, and our results were, as might be expected, encouraging but not elating. The late H. Alistair Reid of the Liverpool School of Tropical Medicine told me that he used twice the number of vials of antivenin for a specific degree of severity of snakebite in 1983 as he did in 1963. My own practice over 30 years reflects a similar course.

If one considers that 25% of all crotalid bites do not end in envenomation, and another 15% are so trivial that they require no more than cleansing the wound, applying a dressing, and giving the appropriate antitetanus agent, this leaves only 60% of all such bites requiring antivenin. Because few copperhead bites need to be treated with antivenin, it would not be surprising that, if the appropriate data were available, perhaps no more than 50% of all crotalid bites in the United States require antivenin treatment. All cases, however, whether poisoning has taken place or not, should be observed for four hours, and a complete blood count, urine analysis, and clotting screen should be carried out.

Perhaps one of the commonest misunderstandings in treating snake venom poisoning in the United States relates to the advice accompanying Wyeth's antivenin [Crotalidae] polyvalent. The instructions in the brochure regarding *minimal, moderate,* and *severe* envenomations refer to those cases *requiring* antivenin, not to all rattlesnake, copperhead, or cottonmouth bites. In other words, these instructions pertain to those cases in which the attending physician decides that the use of antivenin is indicated.

A questionnaire distributed to 32 physicians throughout the United States who currently treat a sizable number of snakebites indicates that the average number of vials used in minimal envenomations is 7.2, in moderate envenomations 11.4, and in severe ones, 18.6. When antivenin administration was delayed more than four hours, the dose was almost doubled. It is well established that the effectiveness of antivenins is dose- and time-related. In the above survey, immediate reactions were seen in 7% of the patients, but in 3% they disappeared when the antivenin therapy was stopped, diphenhydramine hydrochloride given, and the antivenin administration restarted at a slower rate. Less than 1% of the patients experienced an immediate serious or anaphylactic-"like" reaction. In about 70% of the cases a delayed serum reaction developed, with most cases responding to diphenhydramine, although 7 of 400 patients had to be admitted to hospital and treated with steroids or corticosteroids.

The average hospital stay for antivenin-treated patients in the survey was 3.1 days, while the average duration for those not receiving antivenin was 6.3 days, and that for patients having a fasciotomy, with or without antivenin, was 9.6 days. Hospital costs were obviously much higher for patients having a fasciotomy. There were two deaths in patients who underwent surgical procedures without receiving antivenin.

And what's new in snakebite treatment? With respect to first aid or immediate care, the use of the new Sawyer extractor is certainly to be recommended. Both laboratory studies in animals and field studies in humans have shown that this kit can remove significant amounts of venom if applied within three minutes of a bite. This inexpensive first-aid device is advised for all first responders or those frequenting areas where venomous snakes are highly endemic.

The second advancement in snake venom toxinology concerns a new method for producing antivenins that J. B. Sullivan, MD, and I developed. Far smaller doses of this product are needed than of the conventional antivenins now being produced, and cases of serum reaction should be reduced to less than 1%, if studies in animals are an indication. As is so often the case, unfortunately, it may not be financially feasible to produce this antitoxin.

The articles by Wingert and Chan and by Davidson elsewhere in this issue are important contributions to our knowledge on snake venom poisoning and its treatment, and should be studied by every physician treating snakebite in the western United States. As for what AIDS, cancer, and snakebite have in common, I'll be darned if I know.

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Case Reports

The Efficacy of PI^{A1}-Negative Platelet Transfusion Therapy in Posttransfusion Purpura

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POSTTRANSFUSION PURPURA is an uncommon, immune-mediated acute thrombocytopenia that occurs one to two weeks after a blood transfusion in patients with no previous evidence of alloimmunity or autoimmunity against platelets.[1-4] This syndrome generally occurs postoperatively in elderly patients and produces a mortality rate of 10% to 15%. Most information regarding treatment is based on individual case reports; therefore, no definitive standard therapy can be outlined. Although the pathogenesis of this disorder is almost always related to the presence of the antibody against the platelet-specific PI^{A1} antigen,[1-5] the use of a PI^{A1}-negative platelet transfusion is generally not considered effective.[2,3,6-8] We know of only four cases, however, in which PI^{A1}-negative platelet transfusion therapy has been attempted, and the results have been conflicting.[2,6-8] Herein we describe an effective treatment of posttransfusion purpura with the use of PI^{A1}-negative platelet transfusion and discuss factors that may affect the success of this therapy.

Report of a Case

The patient, a 69-year-old woman, was admitted to hospital for a coronary artery bypass graft reoperation. The medical history was notable for three uncomplicated pregnancies and a coronary artery bypass graft six years earlier requiring multiple transfusions. Her medications included nifedipine, propranolol hydrochloride, diazepam, quinidine and nitroglycerin. No abnormalities were found on physical examination. The findings of a laboratory evaluation, which included complete blood counts, were within normal limits.

Because of excessive bleeding from the adhesions and scar tissue in the operative site, she received nine units of whole blood, four units of fresh frozen plasma and six units of random donor platelets. During the operation we noted a transient thrombocytopenia typical of that occurring in patients with extracorporeal circulation and hemodilution, which resolved completely five days later. The surgical procedure was complicated by an embolic cerebrovascular accident (CVA) with vocal cord paralysis. Subsequent difficulty mobilizing pulmonary secretions led to a tracheostomy on the fifth postoperative day, at which time two units of packed red cells were transfused. Although clinically stable, she required two units of Jk^a-negative packed red cells three days later because of an asymptomatic delayed transfusion reaction caused by an anti-Jk^a antibody. Over the next two to four days, six units of fresh frozen plasma, nine units of random donor platelets and two units of packed red cells were administered because of continued oozing from the tracheostomy site. The platelet estimate remained unchanged (median 75,000 per μl) after the random donor platelet transfusion. The prothrombin time, partial thromboplastin time and levels of fibrinogen and fibrin-split products were within normal limits. The platelet count was estimated to be decreased.

Several days later spontaneous petechiae developed, and the presence of thrombocytopenia was confirmed (Figure 1). At this time platelet antibody and antigen testing showed that the patient's platelets were PI^{A1}-negative and her serum contained an anti-PI^{A1} antibody; no other platelet, lymphocyte, granulocyte or drug antibodies were detected. Earlier blood specimens were subsequently retrieved for testing, and the laboratory data from these tests are shown in Figure 1 and described in the Results section. Because the patient was elderly, recovering from an open-heart procedure complicated by a CVA and bleeding from mucocutaneous sites of trauma, such as the tracheostomy site, one unit of PI^{A1}-negative platelets from a single apheresis donor was transfused four days later. The one-hour posttransfusion platelet increment was greater than 80,000 per μl, and no further clinical bleeding occurred. The patient's platelet count decreased

ABBREVIATIONS USED IN TEXT
CVA = cerebrovascular accident
HLA = human leukocyte antigen

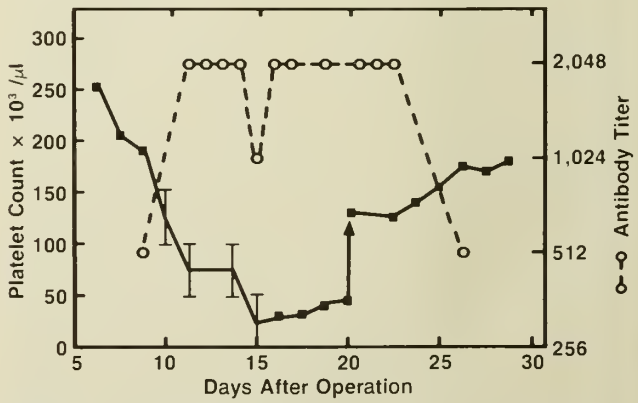

Figure 1.—The graph depicts the clinical course of the patient with posttransfusion purpura. Note the excellent response to PI^{A1}-negative platelet transfusion despite the presence of a high-titered (2,048) anti-PI^{A1}. Anti-PI^{A1} was first detected on the 8th postoperative day. ↑ = One hour posttransfusion platelet count after a transfusion of PI^{A1}-negative single-donor-platelet apheresis equivalent to 6 to 8 units of platelet concentrate. I = Exact platelet count not available; this is a semiquantitative estimate from the peripheral blood smear. The platelet count curve is drawn through the median of the range for which these estimates have previously been standardized.

(Lippman SM, Lizak GE, Foung SKH, et al: The efficacy of PI^{A1}-negative platelet transfusion therapy in posttransfusion purpura. West J Med 1988 Jan; 148:86-88)

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slightly over the next two days, but then steadily increased and remained normal during the next six weeks of observation.

Materials and Methods

Pools of serum from male AB donors were used as negative controls. Serum specimens were taken from the patient at the times noted, and the serum was stored at −76°C. Typing serum was from the reagent collection of one of us (F.C.G.).

As we reported previously,[9,10] the C-FDA and KC-FDA thrombocytotoxicity assays were done to test for Pl^{A1} antigen and antibody and other antiplatelet alloantibodies or drug-related antibodies. One μl of platelets labeled with the vital dye carboxyfluorescein diacetate was dispensed into standard tissue-typing trays preloaded with relevant sera. After the first incubation at 37°C for 30 minutes, the platelets were washed three times (in the trays) with a phosphate-buffered saline solution. One μl of an appropriate dilution of goat anti-human light chain (κ) was added to each well and incubated for two minutes at room temperature. Complement (fresh frozen rabbit serum) was then added, and after it had incubated for 90 minutes at room temperature, test results were read under low-power fluorescence microscopy with appropriate filters for fluorescein excitation. Wells were considered positive if their visibility was at least 50% less than that of the AB control well.

The procedure described above was also used to test for drug antibodies, except that 1 μl of 1 mg per ml of suspension of the appropriate drug was added to the relevant sera in the wells. If cell lysis occurs in wells with added drug but not in control wells, this indicates the presence of drug-related antibodies.

Fluorochromasia lymphocytotoxicity testing was also done, as reported previously by us and others.[9,11]

Erythrocyte serologic techniques followed the standard blood bank procedures of using a solution of low ionic strength or routine saline, albumin or enzyme techniques.[12]

Results

When tested for antibody specificity, serum specimens collected on several postoperative days, as indicated in Figure 1, were strongly reactive with 20/20 Pl^{A1}-positive panel platelets and nonreactive with 9/9 Pl^{A1}-negative panel platelets. Anti-Pl^{A1} titers are also shown in Figure 1 and range from 512 to 2,048.

Tests for thrombocytotoxic antiquinidine antibodies were also negative. No anti-human leukocyte antigen (HLA) antibodies were detected when serum (from postoperative days 10, 15 and 22) was screened against a panel of 60 HLA-typed lymphocytes. The patient's HLA type was A1, A3, B8, B35, Bw6. Crossmatches of her serum with the Pl^{A1}-negative platelets of her apheresis donor were negative.

As seen in Figure 1, transfusion of Pl^{A1}-negative platelets produced a therapeutic posttransfusion platelet increment (80,000 per μl at one hour) even at a time when the patient's anti-Pl^{A1} antibody titer was 2,048; this increment was associated with a definite clinical response of hemostasis with no adverse reactions.

Discussion

Posttransfusion purpura is a self-limited disorder with a median duration of thrombocytopenia of about three weeks when untreated.[1-4] It is, however, potentially lethal, with an estimated mortality rate of 10% to 15%, and can cause significant morbidity, making the initial choice of therapy critical. Although most cases are related to alloimmunization and alloantibody formation against the high-frequency, platelet-specific antigen Pl^{A1}, the role of Pl^{A1}-negative platelet transfusions is uncertain.[2,3,6-8,13] In neonatal isoimmune thrombocytopenia caused by an anti-Pl^{A1} antibody, Pl^{A1}-negative—such as maternal—platelet transfusion is uniformly effective.[4]

The present case conforms to the typical clinical pattern of posttransfusion purpura: an older woman belonging to the 2% to 3% of the Pl^{A1}-negative population, who was probably sensitized to the Pl^{A1}-antigen during her pregnancies or previous transfusions and in whom thrombocytopenia developed one to two weeks after a recent transfusion. She had a definite therapeutic response to the Pl^{A1}-negative platelet transfusion as shown by the greater than 80,000 per μl posttransfusion increase in platelet count within an hour and cessation of mucocutaneous bleeding. Furthermore, her response occurred only one week after the onset of thrombocytopenia and in the presence of a high titer of circulating anti-Pl^{A1} antibodies (Figure 1). Although her counts appeared to be increasing gradually, it is evident that her recovery was greatly accelerated by the Pl^{A1}-negative platelet transfusion.

Including the present case, the use of Pl^{A1}-negative platelet transfusion has been reported in only five patients,[2,6-8] two of whom had definite responses indicated by an increased platelet count or cessation of bleeding, or both (this case and that reported by Le Roux and co-workers).[7] Based on the two responding patients, it seems reasonable to use Pl^{A1}-negative platelet transfusion in patients like these who had no HLA antibodies or febrile transfusion reactions (which may indicate the presence of leukocyte antibodies).[14-17]

Although the number of reported cases is small, a response rate of 40% (two of five) at the very least is promising. The inefficacy of Pl^{A1}-negative platelet transfusion in the three nonresponding patients may reflect factors such as an unrecognized heterogeneity of Pl^{A1} antigen (or antibody) or coincident antibodies to non-Pl^{A1} and possibly to nonplatelet antigens. Because Pl^{A1}-negative platelet transfusion has the potential of giving immediate benefit and is relatively safe, a therapeutic trial of this therapy in patients with posttransfusion purpura is justified. Further studies are needed to ascertain which patients present the best profile for receiving Pl^{A1}-negative platelet transfusion therapy.

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Vitamin A Intoxication Presenting With Ascites and a Normal Vitamin A Level

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VITAMIN A SUPPLEMENTATION by health practitioners and the nonmedical public is becoming increasingly common. Unfortunately, the toxic risks of taking vitamin A are often not appreciated. We report here a case of vitamin A intoxication that was unusual in presentation, with ascites and a normal serum vitamin A level on initial determination.

Report of a Case

The patient, a 3-year-old girl with failure to thrive, was seen after two months of lower extremity pain, periods of refusing to walk, irritability, lethargy, bleeding gums, peeling erythematous skin, pruritus and a protuberant abdomen. On physical examination her vital signs were normal, she was thin and irritable and had mild abdominal distension. Her weight was 11.0 kg (24 lb) and height 84 cm (33 in), both below the fifth percentile. Her head circumference was at the tenth percentile. She showed no abdominal organomegaly nor a fluid wave, and there were no joint abnormalities. The skin was somewhat dry, and results of the rest of the examination were normal. All of the following studies elicited normal values: a complete blood count, platelets, erythrocyte sedimentation rate (ESR), serum alanine aminotransferase (ALT [formerly SGPT]), calcium, uric acid and electrolytes. A urinalysis, urine culture, sweat chloride test and Epstein-Barr virus and cytomegalovirus titers were also negative. A plain film of the abdomen was normal.

After two weeks of observation, she was admitted to hospital because of ascites with respiratory distress. Her weight was 12.6 kg (27.8 lb), her temperature 38.0°C (100.4°F), respiratory rate 30 per minute, heart rate 120 beats per minute and blood pressure 110/60 mm of mercury. New physical findings included a greatly distended and tense abdomen without liver or spleen enlargement, a prominent venous pattern on the abdomen, decreased breath sounds and rales in the right lower lung field, a dry and erythematous skin and brittle hair with alopecia. The extremities were normal with a full range of motion and without pain. Except for irritability, no abnormalities were found on neurologic examination. The fundi were normal.

A paracentesis showed clear and yellow fluid, a leukocyte count of 80 per μl with no polymorphonuclear neutrophils, erythrocytes 510 per μl, glucose 9.0 mg per dl, protein 3.4 mg per dl, albumin 2.3 mg per dl, amylase 14 IU per liter and lactic dehydrogenase 221 IU per liter. The fluid specimen was negative for bacteria, acid-fast bacilli and fungi, and cytologic tests were negative. Blood studies showed the following values: aspartate aminotransferase (formerly SGOT) 80, ALT 31 and alkaline phosphatase 153 IU per liter; total protein 5.2 mg per dl, and albumin 3.4 mg per dl. Results of all of the following studies were normal: prothrombin time; partial thromboplastin time; serum levels of electrolytes, creatinine, calcium, phosphate, uric acid, and amylase; ESR; fluorescent antinuclear antibody, C3 and C4 levels; DNA binding, quantitative immunoglobulins, and a bone marrow biopsy. Tests for tumor markers were negative.

A chest x-ray film showed a normal-sized heart and a right pleural effusion. An abdominal ultrasonogram and a body computed tomographic scan showed massive ascites, a normal liver and spleen, a soft tissue mass in the region of the head of the pancreas and a small calcification in the upper pole of the right kidney. Bone and liver-spleen scans were normal. A lymphangiogram and a nuclear scan study using technetium Tc 99m-labeled antimony showed no lymphatic leakage into the peritoneal cavity.

Upon further discussion, the parents reported that a chiropractor had prescribed vitamin A supplementation seven months earlier because of poor weight gain and eczema. The vitamin A was given at a dose of 100,000 IU per day for one week, then 50,000 IU per day for the following six months, ending one month before her presentation. By history, no other vitamin supplementation had been given. The patient was evaluated for vitamin A toxicity. Long-bone radiographs were normal. Serum vitamin A and carotene levels were 196 IU per dl (normal 65 to 275) and 17 μg per dl (normal 50 to 300), respectively.

An exploratory laparotomy was done because of a suspected intra-abdominal tumor. It showed normal liver, spleen, kidneys, reproductive tract, pancreas, and lymph nodes. There was no inflammation of the serosal surface. A portal venogram showed a hepatic wedge pressure of 150 mm of water (upper limits of normal for adults) and no evidence of obstruction. A liver biopsy specimen showed mild patchy centrilobular sclerosis around the central vein, pericellular sclerosis surrounding individual hepatocytes, and focal prominence of Ito cells shown by fluorescence microscopy. There

ABBREVIATIONS USED IN TEXT

ALT = alanine aminotransferase
ESR = erythrocyte sedimentation rate
RBP = retinol-binding protein

(Mendoza FS, Johnson F, Kerner JA, et al: Vitamin A intoxication presenting with ascites and a normal vitamin A level. West J Med 1988 Jan; 148:88-90)

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were no signs of inflammation. These findings were interpreted as consistent with, but not diagnostic of, vitamin A intoxication.

The patient's postoperative management consisted principally of diuretic therapy, fluid restriction, and nutritional supplementation. Vitamin A intake was minimized. After eight weeks of therapy the patient experienced worsening dermatitis, fissured lips, increased hair loss, irritability, and tenderness of the extremities. A repeat vitamin A level was 838 IU per dl, confirming the diagnosis of vitamin A intoxication.

To increase vitamin A mobilization by increasing the retinol-binding protein (RBP) level,[1] prednisone therapy was started at 2 mg per kg of body weight per day. Table 1 shows the patient's levels of vitamin A, retinol-binding protein, and carotene throughout the hospital stay. After starting the prednisone therapy, the patient's symptoms worsened. A vitamin A level two weeks later was 547 IU per dl, with an elevated RBP value at 11.7 mg per dl. At that time, tapering of the prednisone dose was begun. A week later the serum vitamin A level was 247 IU per dl and RBP 11.5 mg per dl, and total parenteral nutrition was added. The patient began to show decreasing ascites and resolution of her other symptoms. Over the next four weeks all diuretic therapy was stopped, and her ascites stabilized at a minimal level, allowing her to resume normal activities and to be discharged. Five weeks after discharge, the administration of prednisone was stopped, the vitamin A level and RBP levels were normal, and the ascites had resolved. During the subsequent year, she had no recurrence of her ascites.

Discussion

Chronic vitamin A intoxication was well described by Oliver in 1958.[2] The usual presenting symptoms are bone pain; irritability; anorexia; poor weight gain; dry, erythematous, peeling skin; fissured lips; bleeding gums; dry, brittle hair, and alopecia.[2,3] Hepatosplenomegaly has been a common finding; results of liver function studies, however, are usually only mildly abnormal.[2-5] Ascites as a presenting finding has been reported only twice before in children, and in both cases the child had received 100,000 to 300,000 IU of vitamin A per day for more than a year.[6,7] In each of these cases, a liver biopsy was used to confirm the diagnosis, and in one case the hepatic vitamin A content was determined and found to be elevated. Pathologic changes included sclerosis around the central vein, the perisinusoidal areas, and around the individual hepatocytes. The perisinusoidal fat-storing cells, or Ito cells, were prominent in both cases.

TABLE 1.—*Vitamin A, Retinol-Binding Protein (RBP) and Carotene Levels in a 3-Year-Old Girl With Vitamin A Intoxication*

Week	Clinical Course	Vitamin A, IU/dl*	RBP, mg/dl†	Carotene, μg/dl‡
1	Admission long-bone x-ray films normal	...	...	...
2	Laparotomy	...	...	...
3	Peripheral hyperalimentation	...	...	...
4		196	...	17
8	Start prednisone daily dose	838	...	50
10	Prednisone dose tapered	547	11.7	70
11	Start total parenteral nutrition	249	11.5	38
12	Decreasing ascites	269	...	37
14	Decreasing ascites	401	5.1	25
15	Discharge	...	...	...
20	Off steroid therapy	109	4.4	75

*Normal 65 to 275 IU/dl.
†Normal 2.6 to 7.7 mg/dl.
‡Normal 50 to 300 μg/dl.

In the present case, the child had had symptoms before admission that were consistent with chronic vitamin A intoxication. The 50,000 IU of vitamin A per day for six months was a lower intake than previously reported with ascites. A case report, however, of a 6-year-old boy with protein-calorie malnutrition who had a toxic reaction after receiving 20,000 IU of vitamin A per day for more than a year[8] indicates significant variation in the toxic dose.

Even with the history and clinical symptoms, the diagnosis was initially elusive. Long-bone x-ray films and the initial vitamin A level were normal. It was only after the child received nutritional supplementation (with minimal vitamin A intake) that her serum vitamin A level rose into a clearly toxic range. The diagnosis was thus established by the history and clinical symptoms, the elevated vitamin A level, and the liver biopsy specimen showing the histopathologic features of vitamin A intoxication. Reviewing other published cases indicates that establishing a diagnosis of chronic vitamin A intoxication can be difficult without a knowledge of the kinetics of vitamin A metabolism.

Vitamin A is absorbed from the intestine in various forms and transported to the liver for storage, presumably in the Ito cells.[9,10] In the transfer of vitamin A from the liver to the peripheral tissues and to the kidney for catabolism, it is carried by retinol-binding protein as retinol in a 1:1 molar ratio.[1] The binding of RBP to retinol restricts its activity to the appropriate site of action. Unbound circulating retinol leads to the toxic symptoms of vitamin A overload that are thought to be a result of retinol's surface-active and membranolytic effects.[1,11] Smith and Goodman observed that it was the molar ratio of retinol to RBP, and not the absolute level of vitamin A in the serum, that determined whether symptoms of intoxication occurred.[11] A molar ratio of greater than one, indicating the presence of unbound retinol, was associated with toxic symptoms. Furthermore, with low levels of RBP, high levels of vitamin A can exist in the liver because of decreased transport and result in low or normal vitamin A levels in the serum.[1,6]

Retinol-binding protein is produced in the liver and associated with the microsomes. Its release from the liver is partly determined by vitamin A intake. In the presence of liver disease or protein-calorie malnutrition, however, this response is decreased because of a presumed decreased liver production of RBP. In this situation, release of vitamin A from the liver is also impaired. It is possible that in the present case, the child's poor nutritional state may have led to a decreased mobilization of vitamin A from the liver and an initial normal serum vitamin A level. Once her nutrition improved, the vitamin A was mobilized and the level rose.

Although the vitamin A supplementation had been stopped a month before admission, the child's condition worsened with the development of overt ascites. It has been proposed that this delay in the onset of ascites is due to the effects of high-dose vitamin A administration on the liver, which appears to result in enlarging and transforming the Ito cells.[9,10] The enlargement caused by vitamin A in these cells decreases the sinusoidal spaces. Later, fibroblastic transformation of the Ito cells leads to a fibrocongestive hepatic lesion and ascites. This is presumed to be a dose- and time-related

phenomenon and may not lead initially to enlargement of the liver.

Given the worsening nature of the patient's ascites after vitamin A intake was discontinued, a way was sought to maximize the removal of the vitamin A by increasing the RBP levels. Nutritional supplementation was given to provide an adequate protein intake. A trial of prednisone was used to increase the mobilization of hepatic vitamin A by increasing the release of RBP from the liver.[1,12]

In summary, this case report describes an unusual presentation of chronic vitamin A intoxication. It suggests that children with malnutrition may be at a greater risk for intoxication because of impaired RBP production and can present with normal vitamin A levels. Determining the retinol-binding protein level is vital in the diagnosis and helpful in deciding the management. Last, although most patients' symptoms resolve simply by withdrawing the vitamin A supplementation and providing good nutrition, a trial of steroids may be considered in patients with persistent clinical symptoms.

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Dysgonic Fermenter-2 Infections

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Dog bites have been known to cause dangerous sepsis. The most commonly known bacterium is *Pasteurella multocida*. A search of the English language literature was made using MEDLINE 1977-1986 files. Since 1976 there have been multiple reports of dysgonic fermenter (DF-2) infections, many of them following dog bites or casual exposure to dogs. Dysgonic (Greek *dys*, "difficult," plus *gonikos*, "seed, offspring") fermenters are fastidious gram-negative rods easily missed by routine culture media. They are found in the oropharynx of some dogs. Patients with the worst prognosis tend to have splenectomies, alcoholism, or chronic obstructive pulmonary disease.

(Perez RE: Dysgonic fermenter-2 infections. West J Med 1988 Jan; 148:90-92)

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ABBREVIATIONS USED IN TEXT

DF-2 = dysgonic fermenter
HIA = heart infusion agar

There have been 42 previously documented cases of DF-2 infections (one of them presumptive). The clinical spectrum has ranged from self-limited disease to fatal sepsis. The actual incidence is predictably higher than reported because of the difficulties with culture. DF-2 needs enriched media for growth and fermentation. Previous strains have reportedly been susceptible to penicillin. This is the first case description of penicillin resistance with DF-2.

Report of a Case

The patient, a 65-year-old man, had suffered from chronic obstructive pulmonary disease, nephrolithiasis, and hypertension. He was bitten on the left third finger by a dog on March 9, 1986. The following day he described shaking chills and on March 11 had temperatures up to 40°C (104°F). He was admitted to hospital the next day with a blood pressure of 85/70 mm of mercury, confusion, and fecal incontinence. The skin was acrocyanotic with ecchymotic, purpuric, and petechial lesions involving the extremities, face, and periumbilical area. Gangrene developed on the bitten finger without evidence of osteomyelitis. There were no mucosal or retinal lesions. The lungs were clear, and the heart had a II/VI systolic murmur at the apex and aortic valve area. The abdomen was soft without tenderness or organomegaly. There was no costovertebral angle tenderness despite complaints of back pain.

Initially the prothrombin time was 22 seconds, partial thromboplastin time 100 seconds, platelet count 14×10^9 per liter (14,000 per μl), hematocrit 0.39 (38.7%), and hemoglobin 8.4 mmol per liter (13.5 grams per dl). The leukocyte count was 6.6×10^9 per liter (6,600 per μl), with 0.54 (54%) neutrophils, 0.32 (32%) bands, 0.07 (7%) lymphocytes, and 0.06 (6%) metamyelocytes. Serum electrolyte values were normal except for a bicarbonate of 12 mmol per liter (12 mEq per liter). The blood urea nitrogen level was 22.1 mmol per liter (62 mg per dl) and the serum creatinine level 475 μmol per liter (4.2 mg per dl).

The patient was treated with a regimen of penicillin G benzathine, 12 million units per day, and ceftizoxime sodium, 6 grams per day, given intravenously. He became more alert, and his hemodynamic indicators improved after fluid replacement and correction of the metabolic acidosis.

On March 15, he had a respiratory arrest requiring assisted ventilation. His condition continued to deteriorate, and he died on March 18, nine days after the dog bite. The main autopsy findings included a hemorrhagic spleen, congestion of the entire mucosa of the small and large intestines, and mucosal edema and hemorrhage of the major bronchi. The thyroid, adrenal, and pituitary glands were edematous.

All the blood cultures from admission became positive in 48 hours (March 14), with a fastidious gram-negative rod by the Bactec 6A automated system (Johnstons Laboratories, Townson, Md). A preliminary identification of DF-2 was made on March 17, 1986, and was later corroborated by the State of California Microbial Diseases Laboratory. Its growth

requirements and biochemical pattern (Table 1) are similar to the previously reported DF-2. The organism does not grow on MacConkey agar or unsupplemented broth. Growth occurred in enriched chocolate agar (gonococcal agar, hemoglobin, reagents for *Neisseria* and *Hemophilus influenzae*) and blood agar (tryptic soy agar plus 5% sheep erythrocytes), both supplied by Remel Laboratories, Lenexa, Kansas. Repeat cultures after antibiotic therapy was begun remained negative.

The antibiotic susceptibility pattern is different from that in previously reported cases of DF-2 infection. Because of poor growth on routine media, the broth-disk elution method for anaerobic bacteria described by Wilkins and Thiel[1] was used. This patient's bacteria were susceptible to chloramphenicol (12 μg per ml), ceftizoxime (18 μg per ml), and metronidazole (16 μg per ml), but not to penicillin (2 units per ml), clindamycin (1.6 μg per ml), or erythromycin (3 μg per ml).

TABLE 1.—*Characteristics of Bacteria in Patient With Dysgonic Fermenter-2 Infection*

Morphology	Long, thin, spindled gram-negative rod
Catalase	+
Oxidase	+
Growth	
MacConkey agar	–
SS agar	–
Blood and chocolate agar	
25°C (days)	+ (2-4)
35°C (days)	+ (2)
42°C	–
Aerobically	+
Carbon dioxide 5%	+
Fermentation	
Phenol red broth + rabbit serum	
Glucose (days)	A (2)
Lactose (days)	A (3-5)
Maltose (days)	A (3-5)
Triple sugar iron	
Slant/aerobic	Aw
Butt/anaerobic	–
Hydrogen sulfide	–
Lead acetate	+

A = acid; Aw = acid, weak reaction

Discussion

The first report of a case of DF-2 infection was published in 1976 by Bobo and Newton.[2] The following year 17 cases, including that of Bobo and Newton, were reviewed by Butler and co-workers.[3] An additional 25 cases have been reported in the English literature.[4-26]

Most reviews of animal bites fail to recognize DF-2 as a pathogen. In a previous evaluation of canine oral flora, DF-2 was not detected.[27] In two reported cases DF-2 was recovered from the dogs' gingivae.[8,26]

The clinical presentations of documented cases include self-limited infections without the need of antibiotics,[9] cellulitis, gangrene, blepharitis,[25] arthritis, endocarditis[15] without fevers,[10] meningitis,[2,12,26] brain abscess,[16] disseminated intravascular coagulation, the Waterhouse-Friderichsen syndrome,[11] myocardial infarction,[23] and cardiopulmonary arrest.

Of the 43 cases, 24 (56%) were directly related to dog bites and others were associated with dogs. An underlying disease was present in 33 patients (77%). Splenectomy was noted in 17 patients (40%) and alcoholism in 10 (23%).

The overall mortality is 12/43 (28%). Nine of the deaths (9/12, or 75%) occurred in patients with some underlying disease. Conversely, 24 of 33 patients (73%) with underlying illness survived. Three of ten patients (30%) without underlying illness died. In four of ten patients (40%) who died, smears of their peripheral blood or buffy coats showed bacteria. There is no apparent element that correlates with the prognosis. It remains to be proved if the fatal cases are due to penicillin resistance or to a more virulent strain of DF-2.

The optimal culture medium for DF-2 has not been determined. The use of enriched chocolate and blood agar facilitated growth of the strain reported here. Fermentation reactions were possible by adding rabbit serum to the broth (Table 1). Different blood culture media have been used to recover DF-2. These include Bactec 6A, 6B aerobic bottles, 7C anaerobic bottles, trypticase-soy with sodium polyanethol sulfonate, supplemented peptone, and glucose broths. Subculture media have included heart infusion agar (HIA) with 5% rabbit blood in CO_2, trypticase-soy agar with 5% sheep blood, and HIA with 5% sheep blood.[28,29]

Penicillin has been described as the drug of choice, but, as with this patient, one must be aware of resistant strains that until now had not been described. The routine methods for antibiotic susceptibility tests—Kirby-Bauer, minimum inhibitory concentration with Mueller-Hinton broth, and so forth—are standardized for rapidly growing aerobic or facultative organisms. Slow-growing bacteria like DF-2 require modified techniques that allow adequate growth of the organism to detect any effect by the antibiotic being tested. The original strains of DF-2 described by Butler and associates[3] were tested by an agar dilution method using a special medium (Schaedler's). In most of the subsequent reports on DF-2, the authors failed to do or to report their susceptibility tests, sometimes only quoting the previous results of Butler and colleagues. Many community hospitals are not properly staffed or familiar with the technique of diluting agar for fastidious bacteria.

Broth-disk elution tests, such as Wilkins-Thiel's, are easier to do, are reproducible, and are more acceptable to laboratories with limited resources. Antibiotic disk(s) are diluted with broth in individual tubes. For penicillin, a 10-unit disk is diluted with 5 ml of medium, giving a penicillin concentration of 2 units per ml. One drop of bacterial inoculum is added to each tube containing antibiotic and to a control tube without antibiotic. The tubes are incubated and their turbidity is compared with the control tube. Susceptibility can be defined as the absence of turbidity. Reports are given as either susceptible or resistant to the given concentration of antibiotic tested.

Using penicillin alone might not be adequate therapy for sepsis following a dog bite. Administering a second antibiotic active against *Staphylococcus* and other gram-negative bacteria is appropriate while awaiting susceptibility studies. A reasonable regimen to treat a suspected DF-2 infection would be penicillin plus a third-generation cephalosporin like cefotaxime or ceftizoxime while awaiting bacteriologic reports. It would be difficult to justify the use of a first-generation cephalosporin as the main therapy for DF-2, considering its clinical failure with *P multocida*, the lack of central nervous system penetration, and the possible diagnoses listed below.

When a patient presents with petechiae, purpura, and ec-

chymosis, the differential diagnosis includes meningococcemia, Rocky Mountain spotted fever, and sepsis in asplenic and immune-compromised patients. The history of a dog bite should suggest the possibility of *P multocida* and DF-2 infections. Penicillin appears to be the drug of choice for DF-2 infections, but susceptibility tests should be done on all clinical organisms for the possibility of a resistant strain. The best alternative for patients who are either allergic to penicillin or who have penicillin-resistant infections is not known.

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Categorization of Hospital Emergency Services

To THE EDITOR: R. Myles Riner, MD, and colleagues are to be commended for their work reported in the November issue, "Categorization of Hospital Emergency Services."[1] Lest we suddenly all jump to the tune of categorization, however, there is something we must realize—no one has demonstrated that for all its cost and trouble, categorization really saves lives and reduces morbidity.

No matter how elegant the categorization scheme, the actual process involves empowering a state or county agency to demand of local hospitals and physicians the filling out of endless surveys and the attending of required meetings, necessitating, in turn, countless hours of administrative and physician time at the local hospital level—time and money that should perhaps be better spent on direct patient care.

In our local area of California, for example, we have had a categorization scheme of sorts since around 1982, when a regional trauma system was set up. Despite this, not one shred of evidence has been published to date showing that our trauma system in a semiurban and rural area of California desert has significantly altered the outcome of even one case. In fact, the local emergency medical services (EMS) agency that spent who knows how many thousands of dollars has been so inept, in the opinion of Riverside County, that the county "seceded" this month from the regional system.

This is the danger of categorization—no matter how well conceived, it fosters government bureaucracy. Let us rather first prove that it really makes a difference to emergency care. Then, even if it does, let us calculate the cost/benefit ratios of this categorization, taking into account physician and hospital time needed to set up the system. Then and only then should we start "categorizing."

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Prognostic Factors in Hypoxic–Ischemic Coma

To THE EDITOR: The Specialty Conference, "The Neurologic Sequelae of Cardiac Arrest," by W. T. Longstreth, Jr, in the August 1987 issue[1] describes the results of the author's multivariable predictive rule in assessing neurologic outcome after cardiac arrest. Analysis of clinical variables, including pupillary reaction to light, spontaneous eye movements, motor response to pain, as well as serum glucose levels, is successful in identifying patients with very good or poor chances of awakening. However, the scale is less reliable in predicting an unfavorable outcome in patients with cutoff scores greater than 4—which occurred in 44 of 217 patients (20%) without missing values.[2] Levy, whose editorial on this subject appears in the same issue,[3] described a 41% incidence of mortality or persistent vegetative state in a subgroup of 210 patients in hypoxic–ischemic coma with intact pupillary responses, flexor motor function or better, and spontaneous eye movements.[4] These results suggest that clinicians cannot accurately predict unfavorable outcome after cardiac arrest from scales that rely upon preserved brain-stem responses.

Because there is selective vulnerability of the adult cerebral cortex to anoxia, some patients are destined to die without awakening despite brain-stem function because they have sustained irreversible destruction of the cerebral cortex or cerebrocortical death. We have found that bilateral absence of cortical evoked responses is an early guide to this condition and reliably predicts unfavorable outcome (T.L. Rothstein, MD, E.M. Thomas, CRET, S.M. Sumi, MD, unpublished data, June 1983 to June 1987) (Figure 1).

Our study investigated 42 patients in hypoxic–ischemic coma to establish prognostic indices. Patients unconscious at least six hours following cardiac arrest were studied clinically and electrophysiologically with electroencephalogram (EEG), brain-stem auditory evoked response (BAER), and median nerve somatosensory evoked potential (SSEP).

Outcomes were characterized by four clinical groups. Twelve patients (29%) awakened and had normal neurologic findings, including normal or rapidly normalizing SSEP. Seven patients (16%) awakened but recovered with varying degrees of motor or cognitive impairment. They had bilaterally delayed central conduction times or reduced amplitudes of cortical response. A third group consisted of 13 patients (31%) with normal brain-stem reflexes who survived 4 to 64 days without awakening. Somatosensory evoked potential measurement was abnormal in all, with absence of cortical responses in eight and delayed or attenuated responses in five. The final group of ten patients (24%) had no brain-stem reflexes, electrocerebral silence, and bilateral absence of cortical evoked responses; this group fulfilled criteria for brain death.[5]

Brain-stem reflex activity and BAER predicted a favorable

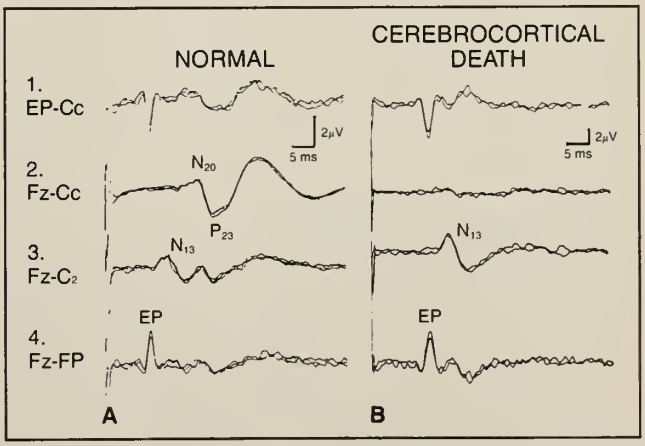

Figure 1.—Somatosensory evoked potentials recorded from the scalp and neck of a normal subject after median nerve stimulation at the wrist **(A)** and from a 78-year-old patient within 24 hours after cardiac arrest **(B)**. In **B** there is preservation of the brachial plexus (EP) and cervicomedullary activity (N13) but no identifiable N20/P23 cortical potential in the F_Z-referenced contralateral cortex (F_Z-C_C) as recorded in channel 2. In addition to pseudolaminar necrosis of the cortex, there was severe neuronal loss in the thalamus at necropsy.

outcome in mild cases and an unfavorable outcome in patients whose responses were absent, indicating brain death, but failed to identify unfavorable outcome in 13 of 42 patients (31%), including 8 patients (19%) who sustained cerebrocortical death. Bilateral absence of cortical evoked responses proved an accurate discriminator. Four patients in this group underwent neuropathologic examination and showed widespread cortical and thalamic destruction, with acute ischemic changes of cortical neurons in those of short survival and frank necrosis of the pseudolaminar type after longer survival.

Patients with bilaterally delayed or attenuated cortical responses had an uncertain prognosis, as some died without awakening. One patient in this group underwent neuropathologic examination and was found to have widespread laminar necrosis with islands of preserved parietal cortex.

Electrocerebral silence reliably predicted unfavorable outcome but was found on initial examination in only 13 of 23 patients (57%) who died without awakening.

Previously reported prognostic factors in hypoxic–ischemic coma such as age, cardiac mechanisms, hypotension, serum glucose levels, and EEG abnormalities other than electrocerebral silence would not have predicted poor neurologic outcome in our patients. While cerebrospinal fluid creatine kinase BB isoenzyme values generally correlated with the extent of brain damage and with neurologic outcome, two of six patients who died without awakening had misleadingly low values.

Our results suggest that conventional scales that rely upon residual brain-stem function will fail to identify patients who have sustained severe and irreversible damage to the cerebral cortex who will not awaken. Bilateral absence of cortical evoked potentials is the most reliable early guide to unfavorable outcome in hypoxic–ischemic coma.

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Public Health in California

To the Editor: Here are two public health concerns that we wish to bring to the attention of your readers.

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Record Increase of Syphilis in California

In the past 18 months, California has experienced a major increase in the number of reported cases of primary and secondary syphilis. Health care providers should be aware of this increase so that appropriate diagnostic and therapeutic interventions can be undertaken.

During the past five years, the incidence of primary and secondary syphilis in California, as a whole, has not reflected the successive yearly decreases that have been reported for the nation. Small fluctuations in incidence were observed from 1982 through 1985, but in 1986 a 35% increase in cases was reported, with a record number of cases (5,897) being reported for the year. Likewise, in the first six months of 1987, reported cases of primary and secondary syphilis were 51% greater than for the first six months of 1986 (3,641 versus 2,412).

TABLE 1.—*Change in Incidence of Primary and Secondary Syphilis From 1983 to 1986 According to Population Group*

Population Group	Change in Incidence: Cases	Change in Incidence: Percent
White males	−1,147	− 55
White females	+ 90	+ 52
Black males	+ 515	+ 52
Black females	+ 544	+233
Hispanic males	+ 435	+ 33
Hispanic females	+ 190	+105

Eight of California's 61 local health jurisdictions reported significant increases (over 20 additional cases) for the first six months of 1987, compared to 1986. These were the counties of Contra Costa, Fresno, Los Angeles, Sacramento, San Bernardino, San Diego, and Tulare, and the city of Long Beach.

Conversely, four major jurisdictions reported significant decreases: the counties of Orange, San Joaquin, Santa Clara, and San Francisco. These reductions were achieved predominantly in high-risk populations—that is, homosexuals or Spanish-speaking undocumented single men (whose infections usually result from sex with prostitutes), or both. Successive yearly decreases have been noted in San Francisco from 1982 through 1986 and have been ascribed to acquired immunodeficiency syndrome (AIDS)-related education campaigns for safer sex practices.

Except for white men, in whom the incidence of primary and secondary syphilis has declined in recent years, increases have been reported in all other major population groups in California since 1983 (Table 1).

Of considerable concern is that case investigations have revealed an ever-increasing association between substance abuse and the incidence of syphilis throughout the state, and, notably, more cases are being identified in young women who engage in part-time prostitution for cocaine—especially "crack" cocaine. The reason for this emerging sex-for-cocaine association probably is due to cocaine's relatively short-lived effect, which requires the user to engage in sex-for-cocaine more frequently. Further, women engaging in part-time prostitution have a greater likelihood of contracting sexually transmitted diseases.

Also of great concern is the sudden and unprecedented increase (79%) in the number of cases of congenital syphilis reported in 1986, with the number of California newborns having definite or probable congenital syphilis rising from 34 in 1985 to 60 in 1986. The increased incidence in black newborns was even more pronounced: 700% (3 cases in 1985 to 24 in 1986). The possible relationship of this to changes in the number of pregnant women having no or delayed prenatal care warrants further investigation. Clearly, practitioners need to perform serologic tests in their pregnant patients, repeating them at each trimester, if indicated, and to be especially vigilant for lesions that might reflect syphilis.

In addition to the concern about congenital syphilis, the increase in primary and secondary syphilis also prompts concern about the control of AIDS, since a history of syphilis is associated with increased risk of human immunodeficiency virus (HIV) infection in both homosexuals and heterosexuals.

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California's Male Suicide Rate at Record High

In 1985, the last year for which complete statistics are available, there were 3,782 suicide deaths among California residents and a record number of male suicides. This is the overall highest number of self-inflicted deaths in California since 1977.

California's 1985 suicide rate of 14.5 deaths per 100,000 population was 0.7% greater than the 1984 rate of 14.4, compared to national suicide rates of 12.0 and 12.3 for 1985 and 1984, respectively. California accounted for 13.2% of all suicides (28,620) in the United States in 1985.

The rise in the number of California suicide deaths was due to an increase in male suicides, with the reported 2,878 male suicides in 1985 being the highest number ever recorded. Conversely, the number of female suicides in 1985 (904) was the lowest ever recorded in California. Similarly, the 1985 California male suicide rate was 22.5 deaths per 100,000 population (the highest rate since 1978), while the female suicide rate of 6.9 per 100,000 was the lowest recorded since 1970. Both of these 1985 rates continued recent trends for California, with the rate for males increasing 3.2% and the rate for females decreasing 4.2%, compared to 1984.

The greatest increase in the number of male suicide deaths was in men aged 65 and older, with the 1985 rates for men aged 65 to 74 and over 75 rising 18.9% and 36.4%, respectively, compared to the 1980 rates. Notable increases in the incidence of suicide in 1985 were also seen among young males, with increases of 7.6% and 46.2% in the age groups 15 to 19 and 5 to 14 years, respectively, although the actual numbers were much smaller than for older men.

In contrast to males, 1985 female suicide rates in California decreased for all ages except older teenagers and women over 75. The rates for these age groups increased from 3.5 to 4.9 deaths per 100,000 and from 9.0 to 11.2, respectively, compared to 1984 rates. The largest decrease (19.7%) was for the 45 to 64 age group, in which the rate dropped from 13.2 to 10.6 deaths per 100,000.

The reasons for the notable increases in male suicides in California during recent years are not clear, and this trend warrants further investigation, especially in regard to preventive interventions.

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Health Care Costs

To the Editor: Our medical care system, like all human endeavor, is not perfect; it shares the problems of our entire economy. What is disturbing in recent years is the widely orchestrated claim of a crisis, allegedly confined solely to health care, with a blind spot for its roots in the more important general economy. A brief look backward into such roots may be helpful in your quest[1] for a different insight into our medical care problems (and perhaps complement your own effort).[2]

Cost comparisons of medical care over time usually end up calling the cost rises "unique" and "monumental," thereby neglecting the historic importance of seven decades of monetary expansion in the entire economy. This refers essentially to the almost constant and progressive loss of the purchasing power of the dollar from such monetary expansion above that calculated for the growth of population and the total economy, innovations, improved technology, and so forth.[3]

In my lifetime, there was a span of years when the total expenditures of the federal government were less than $1 billion a year. Closer to today, federal outlays grew from $33 billion in 1946 to $1.1 trillion in 1986—a 3,200% increase.[4] Almost $3 billion was spent each day by the federal government in 1986. (Incidentally, our indebtedness—overspending—also began in the mid-1940s.) We are not talking about the same dollar then and now. Even calculating "stable" dollars for comparison is subject to error. What we end up with is a continuous cheapening of the dollar. And such cheapening is being done openly now!

Criticism of our medical care system goes back a full century to the time when new (socialist) ideas for reform crossed the Atlantic. The motive has been the introduction of national health insurance. We are reaping the fallout from generations of attacks by advocates of a compulsory public sector program for all. The conflict climaxed with a turbulent array of federal proposals from 1939 to 1961. There was resistance from the public and the American Medical Association, but so many years of repetitious promotion gained a foothold. Despite significant disapproval, Medicare was passed (1965) during the emotional upheaval following President Kennedy's assassination. Further promotion was placed on the back burner when Medicare's problems with understated costs and enormous expansion of demand with rapid increases in such costs began to surface. It was a brief interval, however, and the encounter continued thereafter.

Once-popular comparisons with the British Health Service lost their appeal, but comparisons with the Canadian system promptly filled the gap. Nonetheless, the old conclusion of international comparisons still stands today: "We still have a long way to go in evaluating overall health systems performance."[5] The reason? Lack of completeness of financial data of cost from abroad.

Open advocacy for a national program is at least open and constitutes a legitimate difference of opinion. But it is perplexing to speculate at what is really behind some proposals for cost containment. The links in some argumentative chains could properly be interpreted as an attempt to subvert the foundation of medical insurance.[6] Why? Incentives to what?

Those unable to grasp the enormous probing potential ("outreach") of the federal government to assemble, disseminate, and promote information need to ponder over a 1977 report on national health insurance by the old, familiar Department of Health, Education, and Welfare. What would be different from what we have now? Centralized control (rules and regulations) by the federal government. Regrettably, its performance record is not persuasive, especially since 1977, when the cumulative result of years of overspending and piling

of indebtedness became a crisis of alarm and doom. Is the citizenry eager to generalize the flawed performance of Medicare and Medicaid—the first demonstration of the public sector's capability to fund and administer a national health program?

Medical politics change. The hospitals are not so much the battleground now as is the medical profession. On the one hand we are told we are a business and on the other we are accused of self-interest. Despite two decades of cooperation, compromise, and even submission, we have not fared well with the politicians and bureaucrats who continue their politicized inroads on the authority and autonomy of our professional organizations. We are drifting more and more into political impotence. (It is wearisome to note again that our hands are not clean.)

In this day, where many equate the social and the political, we should be wary of the current fascination with reassessment of the treatment of disease, with the social framework being given singular emphasis. We need to remind ourselves of where government action is necessary and what government does well. There is less doubt that constant improvement or even maintenance of the status quo is no longer a certainty in the standard of health care.[2]

A lot of things cannot be undone—so we are told endlessly. That is a defeatist attitude. In the recent past, the shortcomings of government performance of other services led to efforts to "privatize" them. There is some momentum for this new idea. It is just possible that exploration of cautious and prudent support for and cooperation with the organizations involved in such promotion may offer some defense for preserving private medical care.

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House Staff Well-being

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From a survey of 281 house-staff members of a university medical center, we found that nearly half the respondents were afraid to complain about their training programs and were concerned that their relationship with their partner would not survive the residency. In all, 40% reported that anxiety or depression impaired their performance for a month or more; 12% reported an increased use of alcohol, marijuana, or cocaine; and 7% an increased use of sedatives, stimulants, or opioids. Stressors and dysfunctional behaviors did not differ significantly between male and female house staff, but many women had more tenuous support systems. Married house staff had stronger support systems and less substance abuse, anxiety, and depression. Departments differed widely in house-staff morale, available social supports, and the frequency of dysfunctional behaviors. Residency program directors should assess their house staff's distress and study and initiate means to reduce stress, increase support, and facilitate coping.

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The stress that residency training programs impose on young physicians is not benign. The sequelae include "impairment of patient care, the fostering of poor professional attitudes, and the development of long-term physician dissatisfaction [with medical practice]."[1] Physicians who treat house staff have commented on their distressingly high rates of alcoholism, drug abuse, depressive disorders, and suicide.[2,3] In a survey of substance use among house staff in Boston hospitals, 11% were currently using tranquilizers, 9% opiates, and 9% cocaine.[4] A national survey of internal medicine training programs revealed that about 1% of residents were granted leaves of absence because of emotional impairment; 5% of these residents made suicide attempts and almost half of these were successful.[5]

This report provides cross-sectional data on stressors, support systems, and dysfunctional behaviors from 281 house staff drawn from all hospital departments within a university medical center. The data from distinct subgroups such as married house staff, female house staff—married and single—house staff with children, and those who admitted to substance abuse are presented and their implications explored.

Subjects and Methods

A 37-item questionnaire developed by the authors was distributed to all 401 house-staff members at a university medical center in February 1984, eight months into their residency year. The possibility of winning a cash prize by returning a completed questionnaire facilitated a 70% response rate (n = 281). Residents' anonymity was preserved by requesting coded questionnaires be returned unsigned to the medical center ombudsman's office. Frequency distributions were obtained for responses to all questions, and the data were analyzed using χ^2 tests to explore differences related to gender, marital status, and substance abuse. Because many comparisons were examined, differences significant at the $P = .05$ level may well have been found by chance.

Results

Respondent Demographics and Working Hours

The respondents represented 22 departments or divisions. Response rates varied considerably among departments from a high of 100% in child psychiatry and neurosurgery to lows of 38% in orthopedics and 15% in cardiovascular surgery. The following departments or divisions had 10 or more respondents: medicine (41), pediatrics (32), anesthesia (28), general surgery (20), psychiatry (18), diagnostic radiology (18), obstetrics/gynecology (15), pathology (12), and radiation therapy (10). Of the remaining 87 respondents, 42 were in surgical specialty training programs. Nearly a third (30%) of the respondents were in their fourth or later years of postgraduate training. Their ages were distributed normally with a mean of 30 years (standard deviation = 3.2 years) and a range of 24 to 37 years. Two thirds (67%) of the respondents were men, 22% women and 11% did not answer this question. Of the house staff as a whole, 70% were men and 30% women. Half of the respondents were married and 22% had children (Table 1).

In all, 6% of the respondents were on call daily (!), 33% three or more times each week, 39% twice a week, and the remainder (21%) once a week or less. A third of the respondent house staff "moonlighted," but only 5% (16 members) did so more than eight hours a week.

Stresses Reported by House Staff

One respondent expressed eloquently the stresses of residency training: "Trying to provide personal, conscientious care to patients—that is, living up to my own expectations—while sleep-deprived, poorly nourished, lonely, isolated and feeling unappreciated and at the same time trying to exert some modicum of control over my own life."

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In addition to stresses related to the training program, we assessed those derived from personal relationships, finances, and health. Of the respondents, 14% were very concerned and 32% somewhat concerned that their relationship with their "significant other" would not survive the residency. Almost a third (31%) felt socially isolated.

Professional relationships were also a source of stress for many. Nearly half (46%) of the respondents were afraid they would be labeled "a troublemaker" if they complained about their training programs. Some indicated that this fear had dissuaded colleagues from returning the questionnaire. Only a third were aware of grievance procedures in their department. One in six felt that they could not discuss with faculty attending physicians the issues embedded in prolonging the life of a terminally ill patient or those raised by a patient's death. The overwhelming majority (85%) reported frequently finding themselves with little compassion for patients or using derogatory names in discussing them.

Financial concerns affected 57% of the house staff "very much" or "moderately." One resident, for example, listed his "greatest problem since beginning this training program" as, "family needs, especially financial, must moonlight"; another listed "long hours with relatively low pay for an expensive area."

A third of the respondents had missed work because of illness, but 85% reported working though they would have advised a patient to stay at home. A fourth (26%) were worried about drug abuse by fellow house officers.

Supports Perceived by House Staff

A friend was the most common source of support cited by respondents (68%); family members ranked second (62%). A substantial proportion (27%) of respondents indicated that they had no close friend in whom to confide. Few would seek support from a psychiatrist (16%), faculty member (11%), chief resident (6%), medical center ombudsman (6%), or counselor (4%). Two in five house officers, however, had felt the need for counseling moderately (18%), strongly (12%), or very strongly (10%), but only 2% had received any counseling. Among those experiencing a need, the most common reason given for not seeking counseling was insufficient time (Table 2). Worries about stigma and confidentiality dissuaded about a fifth of respondents. Less than a third (29%) of the respondents could turn for support to a personal physician who was not a fellow house officer.

With regard to support from the faculty, almost two thirds (64%) felt appreciated by faculty members, 79% felt there was a faculty member who would be their advocate if needed, and 63% felt that at least one faculty member represented a "true role model."

TABLE 1.—*Marital Status and Responsibility for Children Among 281 House Officers at a University Medical Center—1984*

	Number		Percent
Married	139		50
With children	56	40	
Without children	81	58	
Unknown	2	1	
Not married	138		49
With children	7	5	
Without children	131	95	
Unknown marital status	4		1
Total	281		100

TABLE 2.—*Reasons for Not Seeking Counseling Among House Officers at a University Medical Center—1984*

	House Officers	
Reason	Male n=161, %	Female n=48, %
No need felt	65	60
No time for regular sessions	20	35
Have to be more seriously disturbed	19	27
Worried about confidentiality	21	13
Worried about the stigma attached	20	10
Financial concerns	16	15
Did not know where to get it	11	15

Psychopathology Possibly Related to Residency Stressors

In all, 40% of the respondents reported being "so depressed or anxious for four weeks or more during my training that my performance was impaired." Substance abuse, defined as the use of illicit drugs, self-prescription of psychoactive drugs, or increased use of alcohol affected a substantial proportion of house staff. Nearly one in eight (12%) reported an increased use of alcohol, marijuana, or cocaine since the start of training; 32% reported a decrease. About 7% reported an increase in sedative, stimulant, or opioid use since training began; 17% reported a decrease. Unfortunately, the questionnaire did not allow respondents to indicate that they did not use drugs; therefore, the "no change" response category included residents who never used drugs together with those whose use continued at a constant level. Drug use in the two categories was significantly related: 79% of those reporting increased use of alcohol, marijuana, or cocaine reported an increased use of sedatives, stimulants, or opioids. Similarly, 98% of those who reported a decrease in the first category reported a decrease in the second ($\chi^2 = 30.4$, degrees of freedom [*df*] = 2; $P < .0001$).

Stressor Disparities in Departments

Large differences were found across departments in house-staff morale, available social supports, and the frequency of pathologic behaviors. To protect confidentiality, specific departments are not identified here. Among those departments with more than ten respondents, fear of being labeled a troublemaker if one complained about the training program ranged from 29% to 67% of respondents. In these departments, 12% to 60% felt there was no faculty role model available and 20% to 88% felt they were not appreciated by the faculty. The proportion reporting increased substance abuse ranged from 0% to 33%. Most departments did not have grievance procedures or problem-solving mechanisms in place, and residents were frequently unaware of those that existed.

Substance Abuse Among Specific Groups of Residents

House staff who increased their drug use had a weaker social support system and a less comfortable relationship with the faculty than those residents whose drug use had decreased (Table 3). Nearly three quarters of those who reported increased drug use (73%) were unmarried as compared with half the respondents as a whole (Table 4). Resi-

TABLE 3.—*Differences Associated With Patterns of Substance Abuse Among House Officers at a University Medical Center—1984*

Descriptor	Substance Abuse: Increased n=33, %	Substance Abuse: Decreased n=90, %	Unchanged Substance Use n=154, %	χ^2*
Often worried that intimate relationship won't survive residency	79	51	47	9.81
Can discuss prolonging patient's life with faculty	70	91	86	8.77
Afraid of being labeled a troublemaker	67	48	41	9.81
Moonlights	67	56	77	9.68
Has a close friend to turn to†	40	70	76	11.73

*$P<.01$, degrees of freedom=2
†Comparison limited to sedative, stimulant, or opioid category only

dents with no children were more likely to have increased their drug use during training than those with children.

House staff whose sedative, stimulant, or opioid use increased differed significantly from those whose use decreased. The former group was more likely to report impairment from depression and anxiety (60% versus 30%, $\chi^2=5.10$, $P<.05$), worry much or most of the time that their intimate relationships would not survive the residency (47% versus 7%, $\chi^2=44.2$, $df=2$; $P<.001$), and lack close friends ($\chi^2=5.96$, $df=1$; $P<.02$).

Female House Officers

The largest percentage of women respondents (n=63) were residents in diagnostic radiology (15%), anesthesia (13%), obstetrics/gynecology (10%), child psychiatry (8%), and pathology (8%). None of the female respondents were in training in neurosurgery, orthopedics, cardiovascular surgery, urology, otolaryngology, or nuclear medicine. The women respondents' age distribution resembled that of the men; slightly more than half were younger than 30 years. No statistically significant differences were found between male and female house staff with regard to stressors such as fear of being labeled a troublemaker or pathologic behaviors such as self-reported anxiety and depression or increased substance abuse. The social support system of many female house officers, however, appeared to be tenuous. Fewer women than men were married (36% versus 54%, $\chi^2=6.23$, $df=1$; $P=.01$). A fourth (24%) of women house-staff members reported worrying much or most of the time that their relationship with their significant other "won't survive the stress of training" compared with 14% of the men. A substantial proportion felt socially isolated (37%), had no close friend (25%), or felt a moderate to very strong need for counseling (40%). Despite the frequent expression of strong need for counseling, only 2% of women house staff actually received it.

The female residents' suggestions for improving the training experience resembled those of the men except that slightly higher percentages of women desired hiring replacements for sick house staff (71% versus 62%), desired "a way not to feel guilty if I can't come in" (66% versus 48%), and suggested increased insurance coverage for counseling (50% versus 41%), counseling at the student health service (48% versus 32%), and support groups (34% versus 25%).

Married House Officers

The proportion of married house officers has increased over the past decade. Half our sample were married (Table 1).

The strength of support systems and the prevalence of emotional distress and increased substance abuse differed significantly between married and unmarried house staff (Table 4). Twice the proportion of unmarried house staff reported feelings of isolation compared with the proportion within the married group. More than a fourth of unmarried house staff worried much or most of the time that their personal relationships might not survive the training period compared with 6% of married house staff. Half of unmarried house staff reported at least four weeks of impairment from depression or anxiety, compared with 30% of married house staff. Three times the proportion of unmarried house staff increased their use of alcohol, marijuana, or cocaine compared with the proportion within the married group.

Married House Officers With Children

Two out of five (41%) married house staff had children, as did 5% of those who were unmarried; of all respondents, 22% had children. Of those with children, 57% had one child, 27% had two and 15% had three or more. Not surprisingly, age was significantly related to being a parent: two thirds of those with children were older than 30 years. We were concerned to find that only 20% of the children of house-staff members had a personal physician other than their parent.

The prevalence of moonlighting increased with family size, probably because of the increased financial needs of

TABLE 4.—*Differences in Stressors, Supports, and Pathologic Behavior Between Married and Unmarried House Officers at a University Medical Center—1984*

Descriptor	Married, n=139, %	Not Married, n=138, %	χ^2
Worried much or most of the time that intimate relationship won't survive residency	6	28	22.79* (df=1)
Felt isolated	21	41	12.47* (df=1)
Felt depressed or anxious 4 weeks or more and had impaired performance	30	50	10.86* (df=1)
Use of alcohol, marijuana, or cocaine			
Increased	6	17	
Decreased	36	29	8.21† (df=1)

df=degrees of freedom

*$P<.001$. †$P<.02$.

larger families. A third to half of those with children moonlighted compared with 25% of married house staff who did not have children. Nearly all (90%) of those who moonlighted eight or more hours a week had children. Although the difference was not statistically significant ($P < .08$), absence from work was twice as frequent among house staff with two or more children than among those with fewer or no children.

House officers with children were less likely to say they had a "close friend" than those with no children (55% versus 78%, $\chi^2 = 8.65$, $df = 1$, $P < .01$), and only 31% with children would turn to "a friend" with serious concerns compared with 69% of those without children. House officers with children were more worried about being labeled a troublemaker for complaining about the training program than those without children (50% versus 33%, $\chi^2 = 5.64$, $df = 1$, $P < .02$).

Discussion

The survey results confirm earlier findings[1,3,6,7] that stressors are plentiful and that persistent, detrimental emotional states are common during the residency experience. The transition from medical student to practicing physician is inherently stressful. A young graduate must master complex new skills: relating comfortably to patients and their families, diagnosing and managing diseases in the face of uncertainty, and accepting responsibility and authority in situations involving pain, disability, and death. Young physicians must also learn to cope with the dysphoria engendered by certain groups of patients.[8] The transition to becoming a physician often occurs simultaneously with other personal sources of stress: geographic separation from friends and family, new marriage, parenthood, and increased worries over accumulated debts.[6] We view residency stressors, after being filtered through individual coping styles and moderated by support systems inside and outside the training program, as contributing strongly to dysfunctional behaviors during the residency and perhaps in later professional life. This formulation, while supported by several studies,[6,9] requires more careful and thorough empiric evaluation.

Increased stress appears to be associated with weaker support systems and more dysfunctional behavior.[9,10] This association and the effect of residents' coping styles on substance abuse, emotional distress or disorder, and satisfaction with professional life on residents' coping styles should be systematically studied. Coping strategies used during the residency may predict a future ability to deal with stress both in the personal and professional arenas,[11] although a recent study found that physicians' coping styles were not closely related to measures of life satisfaction.[12] The effects of sleep deprivation deserve special study because sleep-deprived residents have been found to make more errors on cognitive tasks and to be more depressed and irritable.[13,14] Most interns work 70 to 100 hours a week and are repeatedly required to stay awake for 36 hours or more. The sequelae of sleep deprivation are antithetical to the goals of residency training.[15]

Alcohol and drug abuse both during residency and in later life affect physicians at least as often as the general urban population.[16] Physicians in certain specialties may be at a greater risk of drug abuse and dependence.[17] In the past decade the reality of the "impaired physician" has been recognized.[18] The current loss of physicians to these psychopathologic behavior patterns is a tragic waste of persons who have been trained to ameliorate human suffering.

In this study, the residents who had increased their substance abuse during training appeared to be the most stressed. Because of the cross-sectional nature of our survey, however, we cannot infer the direction of the relationships between stress and substance abuse. Do house staff who are depressed, anxious, socially isolated, or concerned about personal relationships turn to drugs or alcohol (or both), or are these psychosocial states the consequences of substance abuse? In any case, the increased substance abuse and psychosocial morbidity reported by some respondents are cause for great concern.

Of our respondents, 40% reported being sufficiently depressed or anxious for a month or more that their work performance was impaired. This figure is higher than that reported in a study of interns (27%)[3] and much higher than the six-month prevalence figure reported for comparably aged people in the general population (about 7%).[19] Part of the difference probably stems from different case finding and definition methods, but, by any measure, this frequency of depressive and anxiety disorders is alarming. Earlier studies have reported a relationship of depression during residency training to the number of hours worked,[7] to self-reported depression test scores at the start of training, to parental history of depression, and to the presence of a "workaholic personality style."[3] Residency program directors should attempt to replicate and extend these findings about risk factors and should study the effectiveness of preventive interventions.

Marital disruption, although typically ensuing in later years when hoped-for changes have not occurred, often has its roots in the loneliness and frustration of the residency training years.[20,21] Uncontrolled studies suggest that marital therapy and support groups for house officers' spouses may be beneficial, but controlled research is lacking.[22,23] Our results suggest that, contrary to the concern that marriage and residency may not mix, married house staff appear to be coping better with the stresses of training than those who are unmarried.

As in other studies,[5,10] women house staff appeared to have somewhat fewer social supports than their male counterparts and perhaps greater vulnerability to the adverse effects of stress. They reported often feeling (or actually being) excluded from the "fraternity of their male peers." As Rinke[24] has pointed out,

> Many women enter medical school with negative self-images, feeling less adequate than men, and these feelings are projected onto female peers: no woman can be as competent as a man. This unfortunate phenomenon occurs at a time when women could benefit from supporting each other and sharing their common experiences.

Women physicians are at greater risk of committing suicide than male physicians and the general population.[7] The risk is particularly acute among unmarried women physicians. Preventive strategies initiated during residency years deserve urgent study.

The stresses of residency training and their sequelae have been acknowledged increasingly in the past decade. With this acknowledgement has come a number of suggestions for how training programs can reduce unnecessary distress and how residents can better cope with the unavoidable stresses.[1,2,6,25,26] Among the most common suggestions are increasing the interval between on-call nights, establishing a night "float" system, and hiring replacements when house staff are sick rather than increasing the workload of those remaining. Some medical educators are concerned that decreasing the number of on-call nights may impair the quality

of residents' educational experience or simply permit unnecessary moonlighting. The question deserves empirical study, but available evidence suggests that frequent nights on call may impair learning.[13-15] Many moonlighting house staff in our sample appeared to have a genuine need because moonlighting was more common among house staff with family responsibilities.

Other widespread suggestions for reducing stress include providing better career counseling and encouraging discussion with faculty physicians of emotionally draining experiences such as managing "difficult" patients, unexpected deaths, and ethical dilemmas. Suggestions less widely discussed include reducing financial strains by increasing salaries or providing housing subsidies, establishing procedures for house staff to voice dissatisfactions with the training program without fear of reprisal, and creating part-time residency positions for house staff with family responsibilities. All of these suggestions (and others) were voiced by the residents in the present study, and many were incorporated in the final report of the medical center's House Staff Well-being Committee to the dean and hospital administrator.*

Steps to increase the support mechanisms available to residents have also been suggested. The most widely studied intervention has been establishing resident support groups. Anecdotal reports suggest that these are highly beneficial.[1,2,23,27,28] About 40% of residency training programs currently offer some form of support group, the proportion ranging from 20% among surgical programs to 59% in family practice and 68% in psychiatry programs. About 20% of our respondents desired support groups. Some educators favor weekly social get-togethers of house staff and senior faculty to facilitate communication and build morale. More than a third of our respondents wanted counseling, and almost half requested increased insurance coverage for psychotherapy. The intervention most frequently endorsed (by about 75%), however, was hiring replacements when a house officer was unable to work, rather than increasing the work loads of those remaining. Replacements are difficult to find, but fourth-year medical students can take on a limited caseload as externs, house-staff members can be shifted temporarily from lightly used consulting services or electives, and recently established practitioners may have time to assume the care of a number of patients in hospital.

Ziegler and associates[20] have summarized methods for coping more effectively with the unavoidable stresses of residency training. They group coping strategies under the rubrics of recognizing stressors, time management, behavior modification, social supports, environment, and relaxation techniques. Because these coping strategies may reduce morbidity, they deserve wide study and dissemination to house staff. An annual orientation meeting for new house staff could be a useful forum.

The medical profession devotes its energies to preventing, ameliorating, and curing disease. Paradoxically, the profession attends inadequately to these responsibilities for its own members, particularly its newest practitioners. We believe that this neglect stems in part from physicians' and others' resistance to recognizing the importance of mental disorders such as depression and substance abuse and the role of psychosocial stress in their cause. Physicians may also resist acknowledging that we are as susceptible as our patients to stress-related disorders. Preserving elements of "rites of passage" undisturbed and economic concerns of hospital administrators have also been suggested as sources of resistance to change.

Young physicians deserve better care from their mentors. We urge residency program directors to assess the level and sources of distress among their house staff and to initiate and study actions designed to reduce stress, increase support, and facilitate coping.

*M. Allen, MD, A. Barbour, MD, D. Berger, MD, P. Bittner, MD, R. Cutler, MD, S. Donaldson, MD, C. Flexner, MD, K. Marton, MD, M. Miner, MD, R. Rosen, MD, J Stenger, MD, and M. Knox were members of the Committee on House Staff Well-being at our medical center.

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Magnetic Resonance Imaging for Musculoskeletal Disorders

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COMBINING THE SENSITIVITY of scintigraphic techniques with the spatial resolution of computed tomography (CT), magnetic resonance imaging (MRI) has greatly enhanced the detection and determination of the extent of disease processes involving bone marrow. The superior contrast discriminating capabilities of the technique compared with those of CT have also provided new insight into a variety of conditions affecting musculoskeletal soft tissue structures.

MRI has been applied to a broad spectrum of bone marrow disorders, including sickle cell anemia, Gaucher's disease, radiation change and osteopetrosis. The technique has also been used in children to evaluate acute, subacute, chronic and recurrent osteomyelitis. MRI has been shown to be the most sensitive imaging method for the early diagnosis of avascular necrosis, including Legg-Calve´-Perthes disease. It is also sensitive for detecting malignant areas within bone marrow and promises to be useful in assessing and treating hematopoietic disorders. Chemical shift imaging, which selectively evaluates fat and water protons, has been used to evaluate normal bone marrow as well as metabolic, inflammatory, traumatic and neoplastic conditions.

MRI is superior to CT in delineating the extent of musculoskeletal neoplasms and their relationships to surrounding structures. In particular, MRI is a sensitive method of detecting and staging primary bone tumors. For showing the extent of tumor in marrow and soft tissue, the technique is superior to CT in most instances. The method is particularly useful in delineating spinal tumors, including bone involvement, spinal canal invasion, paraspinal soft tissue extension and vascular compromise. Owing to its superior inherent image contrast, MRI is also better than CT in determining the size and extent of musculoskeletal soft tissue masses and their relationships to vascular and nonvascular structures. Improved anatomic information with MRI results from the ability to image in the axial, coronal and sagittal planes.

MRI has been shown to be valuable for a variety of posttraumatic abnormalities affecting the musculoskeletal system. Because of its ability to show small meniscal lesions and ligamentous injuries, surface coil MRI may eventually replace arthrography. The technique can differentiate complete disruption of the patellar tendon from partial tears, ligamentous inflammation and localized effusion of the infrapatellar bursa. Injuries to the collateral and anterior or posterior cruciate ligaments are readily identified by MRI, and the state of synthetic grafts can also be ascertained. The technique can also depict abnormalities at the knee, including degenerative joint disease, osteochondritis dissecans, medullary infarcts, epiphyseal osteonecrosis, intraarticular osteochondral fragments, synovial and subchondral cysts, joint effusions and Osgood-Schlatter disease. In patients with the carpal tunnel syndrome, segmental and diffuse swelling or distortion of the median nerve and thickening of the tendon sheaths may be observed by MRI. In the hands and feet, MRI of tendons has identified acute posttraumatic rupture, acute tenosynovitis, chronic tendinitis and postsurgical complications. The method has significant potential as a noninvasive tool for evaluating traumatized shoulders, being most useful for showing the rotator cuff.

MRI has proved useful for evaluating additional articular disorders in both the vertebral column and appendicular skeleton. Pathologic conditions of the spine including canal stenosis, herniated discs and rheumatoid arthritis have been studied. MRI provides diagnostic information comparable to that of CT or myelography in patients with lumbar disc disease and may become the initial procedure of choice with further technical advances. Postoperative fibrosis can be distinguished from adjacent thecal sac and disc material. The accuracy and sensitivity of MRI are comparable to those of radionuclide scanning in cases of vertebral osteomyelitis. At the knee, intraarticular soft tissue tumors and synovial disease including rheumatoid arthritis have been studied, whereas in the wrist, navicular nonunion or pseudarthrosis, rheumatoid arthritis, recent fractures, ganglions and other soft tissue alterations have been evaluated. Comparison with arthrography, CT and surgical findings has shown that surface coil MRI accurately depicts both normal and abnormal temporomandibular joints.

Disorders of muscle including Duchenne's and other dystrophies, atrophy, amyotrophic lateral sclerosis, sensorimotor neuropathies, cerebral palsy, poliomyelitis and mitochondrial disease have been studied by MRI. Patients with neoplasms, inflammatory disease, retroperitoneal hemorrhage, iliopsoas bursitis and hypertrophy affecting the psoas muscles have also been evaluated. High-resolution phosphorus 31 magnetic resonance spectra have been obtained from normal and pathologic skeletal muscle and from bone tumors of the extremities, providing insight into their physiology.

With regard to the ultimate role of MRI in patients with musculoskeletal disease, it will complement rather than replace existing technologies. Areas of potentially promising clinical application for MRI in the future include quantitative bone marrow densitometry for monitoring infiltrative disorders and possibly metabolic bone disease, three-dimensional image reconstruction and intraarticular administration of paramagnetic contrast agents before examining joints.

(Sartoris DJ, Resnick D: Magnetic resonance imaging for musculoskeletal disorders. West J Med 1988 Jan; 148:102)

From the Department of Radiology, University of California, San Diego, Medical Center.

Reprint requests to David J. Sartoris, MD, Department of Radiology, UCSD Medical Center, 225 Dickinson St, San Diego, CA 92103.

GENERAL REFERENCES

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Petterson H, Hamlin DJ, Mancuso A, et al: Magnetic resonance imaging of the musculoskeletal system. Acta Radiol Diagn (Stockh) 1985 May-Jun; 26:225-234

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Commentary

Strike!

ELLIOTT WOLFE, MD, *Santa Clara, California*

After a Saturday morning of cleaning floors and furniture in our hospital with my colleagues, I predicted that we had reached the midpoint of the strike. Although I usually practice internal medicine and am Director of Staff Education, I was working with other physicians and administrative personnel to keep the Kaiser-Permanente Medical Center in Santa Clara, California, functioning during a recent strike by the members of the Hospital and Institutional Workers' Union. My halfway prediction was off by five days; the strike lasted seven weeks, not six. Just as small but exquisite flowers bloom in the desert and water can taste like wine, adversity may lead to unanticipated accomplishments and joys.

Physicians found themselves functioning as nurses whenever the nursing service needed assistance. One night I was assigned to care for a patient who was on a mechanical ventilator. I had the good fortune to work with a nursing supervisor who was respectful, thoughtful, and caring. She helped me remember many of the techniques of my internship days at Mount Sinai Hospital (New York City) when we did more nursing care than today's resident physicians. Her gentleness with our elderly patient rekindled the deep feelings of admiration that I have always had for nurses. She spoke softly as we were working together to change his bedsheets and bathe him: ". . .now, Doctor, you stand there, and I'll show you this simple trick to change the topsheet. . .," and, ". . .this is my personal favorite mixture of ointment and gum that I use to protect tender skin. . . ." One eight-hour shift with one registered nurse equaled one unparalleled experience for me.

When I worked in the pharmacy, greeting patients and giving them their prescriptions, I felt like the friendly corner druggist of my childhood years in Brooklyn. I thought about the 19th century when physicians did more dispensing than diagnosing, until crusading doctors advocated giving advice and prescribing but not dispensing. Here I was in the surprisingly fulfilling position of doing it all: diagnosing, prescribing, and dispensing.

Instrument Processing is an area in the surgical suite where surgical instruments, towels, and paraphernalia are washed, packaged, and sterilized. In that little enclave, a place I had never entered, I found two new friends—Charlotte and Joan. Working with their hands, dressed in surgical scrubs, they were accomplished raconteurs. Talk fueled their ideas and plans for the future: Charlotte is studying acting and wants to audition for an advertising agency; Joan thinks about franchising stores to sell a gelatin dessert ("Just Jell"), or marketing a message screen that would be placed adjacent to those new eye-level automobile traffic lights. When I discovered that the chief of surgery had his own special tray of instruments ("Porter's Extra"), I decided that I wanted mine, henceforth to be known as "Wolfe's Extra." Charlotte and Joan promised an always-available "sterilized tray" of tablets, pencils, markers, and erasers for the "Chief of Education."

Educational programs were thrown into limbo during the strike—not top priority. We accepted that for about a week and then returned, as much as we could, to the normal pattern of teaching rounds and conferences for medical students and residents. My colleague, Henry, and I used available (minimal) resources and were able to maintain the key components of the educational program for six of the seven strike weeks.

Barbara, my wife of 30 years, volunteered to help in the education office. Although she listened to my stories through the years, patiently attended the annual graduation parties, and often accompanied me to the hospital on weekends for rounds and other responsibilities, Barbara had not worked with me at Kaiser-Permanente during the 17 years that I have been there. We had worked together when I started to practice medicine on Staten Island in the mid-1960s. What a joy it was to have her there to share my educational, administrative, and practice lives! Patients, several of whom had been consulting me for more than 15 years, met my wife for the first time. I was thrilled to be able to introduce her to so many of these "old friends" of our family.

Barbara and I were able to have weekday lunches together and even stole an occasional hug and kiss. During the waning days of the strike, one evening while we were sharing a quiet time before dinner, Barbara said, "I have fallen in love with you all over again, just as when we first met and then when I first saw you practicing medicine."

I have known as a teacher that the unexpected can provide a rare opportunity to teach students about the practice of medicine. A creative and experienced physician sees the spark that ignites the fire. This time, I was the student and the teacher; the strike was the spark.

(Wolfe E: Strike! West J Med 1988 Jan; 148:103)

From the Department of Staff Education, Kaiser-Permanente Medical Care Program, Northern California Region, and the Department of Medicine, Stanford University School of Medicine, Stanford.

Reprint requests to Elliott Wolfe, MD, Department of Staff Education, The Permanente Medical Group, Inc, 900 Kiely Blvd, Santa Clara, CA 95051.

Book Reviews

HERNIA REPAIR WITHOUT DISABILITY—Second Edition—Irving L. Lichtenstein, MD, Fellow, American College of Surgeons, International College of Surgeons and American Association for the Advancement of Science; Diplomate, American Board of Surgery, Pan American Medical Association and National Board of Medical Examiners; Associate, World Medical Association; Founder and Director of the Lichtenstein Hernia Institute. Ishiyaku EuroAmerica, Inc, 11559 Rock Island Ct, St Louis, MO 63043, 1986. 250 pages, $85.

To document the prohibitive cost of the surgical repair of hernias and detail a solution makes Dr Lichtenstein's monograph valuable. To submit research data supporting less costly yet better surgical methods and results makes this book outstanding. To add innovative illustrations that are an integral part of the monograph plus quotations that are collectable makes the publication a "must reading" for surgical residents and should be part of the library of one who has "done hernias for years." Delightful, helpful, and impressive, it has changed my surgical approach and thinking to hernia repair.

JOHN W. BATDORF, MD
Associate Professor of Surgery
University of Nevada School of Medicine
Reno

* * *

PATHOGENESIS OF SKIN DISEASE—Edited by Bruce H. Thiers, MD, Associate Professor of Dermatology, Medical University of South Carolina, and Chief, Dermatological Service, Veterans Administration Medical Center, Charleston, South Carolina, and Richard L. Dobson, MD, Professor and Chairman, Department of Dermatology, Medical University of South Carolina, Charleston. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1986. 623 pages, $95.

Pathogenesis of Skin Disease is a compilation of 40 chapters presented in 13 overall sections and covering 623 pages excluding the index. As the name implies the primary purpose of this volume is to present the state of the art as to the pathogenesis or known mechanisms for the development of a large number of skin diseases. In order to achieve this goal the editors have enlisted the aid of 67 authors including themselves. The 13 sections include (1) allergic and eczematous diseases such as immediate and delayed hypersensitivity responses and atopic dermatitis, (2) pilosebaceous disorders including acne, androgenic alopecia, and alopecia areata, (3) the papulosquamous diseases psoriasis and lichen planus, (4) vitiligo, (5) bullous disorders including pemphigus, pemphigoid dermatitis herpetiformis, herpes gestationis, and acquired epidermolysis bullosa, (6) an extensive eight-chapter discussion of the "connective tissue" and vascular disorders ranging from lupus erythematosus to erythema multiforme, (7) granuloma annulare and sarcoidosis, (8) the porphyrias and hyperlipidemias, (9) infectious diseases, which only covered the acquired immune deficiency syndrome, (10) an extensive section on neoplastic disease with an excellent chapter on Kaposi's sarcoma, (11) certain inherited disorders such as the ichthyoses, epidermolysis bullosa, Ehlers-Danlos Syndrome, and xeroderma pigmentosum, (12) discussion of psychocutaneous problems and (13) wound healing.

Though the use of large numbers of authors leads to irregularity in the presentations, the general presentation is excellent. The name of the volume is misleading in that it does not cover the pathogenesis of skin diseases in general or in all of the parts. Perhaps the inclusion of the pathogenesis of pigmentary disorders other than vitiligo and infectious diseases other than AIDS would have been expected.

However, despite the authors' prediction that the text would be out of date by the time it was published, this book does provide an excellent basis for understanding the new information that will be available to us in the near future on many cutaneous diseases. Since the book is concerned primarily with pathogenesis, it will be of most value to students and practitioners of dermatology. It should be included in the libraries of all dermatology training programs and should be available to practitioners who wish to understand more about the diseases examined. It is not of much practical value to the primary care physician, however, and most likely will be used only by the dermatologic community.

JOHN H. EPSTEIN, MD
Clinical Professor
University of California
San Francisco

* * *

ABORTION, MEDICINE AND THE LAW—3rd Edition—Edited by J. Douglas Butler, DPM, JD, Dept of Orthopaedics, Howard County General Hospital, Columbia, Maryland, and David F. Walbert, JD, Adjunct Professor of Law, Emory University, Atlanta. Facts On File Publications, 460 Park Ave South, New York, NY 10016, 1986. 755 pages, $40.

For the past 20 years in this country abortion has been subjected to protracted public debate and intense medical scrutiny. The concept of legal termination of pregnancy upon request has touched deeply held principles concerning autonomy of women and human rights for the unborn. Our society has become polarized around an issue that has led to intense legislative debate in state capitols and in Washington, DC, as well as violence in and around medical facilities.

Not surprisingly, 80% of this book is directed at the judicial and legislative war of words that has been waged and that will continue for the foreseeable future. The Supreme Court decisions in Roe versus Wade and Doe versus Bolton are presented in full as a part of the appendices, which also include the verbatim testimony before the United States Senate on the Human Life Bill in 1981. Among the legal essays is a chapter on the issue of minors' rights, which is of particular importance to citizens of California because of the recent passage of a parent notification statute, which has yet to be implemented. Interestingly, a Minnesota court has recently overturned a similar bill of long standing, noting that its primary result had been to delay abortion procedures.

The medical aspects of abortion are covered by recognized authorities. Most thorough is a chapter on prenatal diagnosis and selective abortion. With the advent of chorionic villus sampling, earlier diagnosis of genetic problems will allow terminations of pregnancy in the first trimester when morbidity is low and vacuum aspiration more acceptable than second trimester procedures. It is likely that genetic abortions will represent an increasing number of the approximately 1.2 million abortions reported yearly in the United States.

Finally, ethical concepts are detailed, with arguments for and against legal abortion.

This book is a valuable work for any library and for the personal collections of those interested in reproductive rights, especially because primary sources of information are quoted verbatim.

ALAN J. MARGOLIS, MD
Professor
Obstetrics, Gynecology and Reproductive Sciences
University of California, San Francisco,
School of Medicine

* * *

CASARETT AND DOULL'S TOXICOLOGY—THE BASIC SCIENCE OF POISONS—Third Edition—Edited by Curtis D. Klaassen, PhD, Professor of Pharmacology and Toxicology, University of Kansas Medical Center; Mary O. Amdur, PhD, Senior Research Scientist, Energy Laboratory and Department of Applied Biological Sciences, Massachusetts Institute of Technology, Cambridge, and Associate Professor of Toxicology, Harvard School of Public Health, Boston, and John Doull, MD, PhD, Professor of Pharmacology and Toxicology, University of Kansas Medical Center, Kansas City. Macmillan Publishing Company, 866 Third Ave, New York, NY 10022, 1986. 932 pages, $49.95.

A good toxicology text is hard to find! Interest is growing in acute and occupational toxicology, which is often covered only briefly in sections of pharmacology texts. Other textbooks on the subject often focus only on the clinical side and do not provide sufficient basic information. The third edition of this classic text gives the reader much more in-depth information from multiple authors dealing with most but not all areas of modern toxicology. There are major new chapters on biotransformation of toxicants and toxic responses of the immune system, the cardiovascular system, the skin, and the eye. In addition, there are new sections on the toxic effects of plants, analytical toxicology, and regulatory toxicology.

The overall framework of this book is both an asset and a liability. The text is divided into five units: General Principles, Systemic Toxicology, Toxic Agents, Environmental Toxicology, and Applications, and while it does not lend itself readily to answering clinical questions, it does give a much more in-depth view than the other clinical texts. The three primary editors have done an excellent job in editing, giving the text a uniform style. It can be frustrating to read certain parts of the text that are placed in small print and provide very detailed reviews. For the most part the chapters from the second edition, published in 1980, have been updated. Although many of the authors are the same, there are new authors who have added substantially to the importance of this text. Most of the chapters are authoritative and thorough.

It is clear that this textbook is an adjunct to courses in pharmacology and toxicology. It will also be useful to scientists with particular interest in the discipline of toxicology. Since approximately one third of the chapters in this edition have been rotated and broadened, the text is quite up to date and thorough. There is no doubt that this book is a valuable addition for those with an interest in the basic science of poisoning: toxicology.

CHARLES E. BECKER, MD
Chairman
Division of Occupational Medicine
San Francisco General Hospital
San Francisco

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ARIZONA

The following list of continuing medical education programs in Arizona is compiled by the Arizona Medical Association. All courses listed have been certified as meeting the criteria for Category I of the ArMA CME Certificate and the AMA Physicians Recognition Award. To list Category I continuing medical education programs, please send information to Arizona Medical Association, 810 West Bethany Home Road, Phoenix, AZ 85013; or phone (602) 246-8901.

Brochures and registration forms are available from the contact person or organization sponsoring the program.

January 22-24—**14th Annual Sports Medicine Symposium.** Holiday Inn Metrocenter, Phoenix. Fri-Sun. Contact: ArMA.

February 1-3—**State of the Art 2D/Doppler and Color Flow Imaging.** Sheraton El Conquistador Resort, Tucson. Mon-Wed. Contact: American College of Cardiology, (800) 253-4636, ext 226

February 4-6—**14th Annual Frontiers in Ophthalmology.** Scottsdale Hilton, Scottsdale. Thurs-Sat. Contact: Campbell Meeting Management for St Luke's Medical Center, (602) 838-6728.

February 10-13—**Sports Medicine—For All Practitioners.** La Posada Resort, Scottsdale. Wed-Sat. Sponsored by American College of Sports Medicine and Children's Medical Center, Oakland, California. Contact: Stuart C. Zeman, MD, Course Chairman, 2999 Regent Street, #203, Berkeley, CA 94705. (415) 540-8686.

February 25-27—**Contraception, Sterilization, and Sexually Transmitted Disease.** Paradise Valley Resort, Scottsdale. Thurs-Sat. Contact: Robin Murray, American College of Obstetricians and Gynecologists, (202) 863-2543.

February 25-28—**Arizona Academy of Family Physicians Scientific Assembly—1988.** Embassy Suites—The Biltmore, Phoenix. Thurs-Sun. Contact: AAFP, (602) 249-2021.

February 26-28—**Fourteenth Annual Scientific Session of the Arizona Society of Anesthesiologists.** Scottsdale Hilton Resort, Scottsdale. Fri-Sun. Contact: Beverly Richter, Arizona Society of Anesthesiologists, (602) 246-8901.

February 29-March 3—**Practical Radiology.** Loews Ventana Canyon Resort, Tucson. Mon-Thurs. Contact: U of A.

March 2-4—**11th Annual Mid-Winter Symposium in OB/GYN.** Scottsdale Hilton Hotel, Scottsdale. Wed-Fri. Contact: Secretary, Phoenix OB/GYN Society, (602) 241-1917.

March 5—**Current Perspectives: Cancer Screening, Treatment and Followup.** Arizona Medical Association, Phoenix. Sat. Contact: ArMA.

March 6-9—**2nd Annual Barrow Neurological Institute Magnetic Resonance Imaging Conference.** Camelback Inn Resort, Scottsdale. Sun-Wed. Contact: Barrow Neurological Institute, (602) 285-3178 or 1 (800) BARROW-1

March 10-12—**Practical Cardiology for the Family Physician.** La Posada Resort Hotel, Scottsdale. Thurs-Sat. Contact: American College of Cardiology, (800) 253-4636, ext 226.

March 10-12—**15th Annual Symposium: Selected Topics in Ischemic and Hemorrhagic Cerebrovascular Disease.** Camelback Inn Resort, Scottsdale. Thurs-Sat. Contact: Barrow Neurological Institute, (602) 285-3178 or 1 (800) BARROW-1.

March 17-19—**24th Annual Arizona Chest Symposium.** Doubletree Hotel, Tucson. Thurs-Sat. Contact: Susan Thornton, RN, MS, Tucson Medical Center, (602) 327-5461, Ext. 5110.

March 22-25—**Pediatric Update 1988.** La Posada Resort Hotel, Scottsdale. Tues-Fri. Contact: Paul C. Stillwell, MD, Phoenix Children's Hospital, (602) 239-5778.

CONTACT INFORMATION

ArMA—Contact: Arizona Medical Association, 810 W Bethany Home Rd, Phoenix, AZ 85013. (602) 246-8901.

U of A—Contact: University of Arizona College of Medicine, Arizona Health Sciences Center, Tucson, AZ 85724. (602) 626-6707.

CALIFORNIA, HAWAII AND NEVADA

This listing of continuing education programs in California, Hawaii and Nevada is supplied by the Committee on Continuing Medical Education of the California Medical Association. All courses and meetings listed have been approved for Category I credit toward the CMA Certificate in Continuing Medical Education. To have accredited courses listed here, please send information at least two months in advance to Department of Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690; or phone (415) 863-5522. For a list of organizations approved for Category I credit toward the CMA Certificate in Continuing Medical Education or for more information on accreditation or certification, please write to the above address.

KEY TO ABBREVIATIONS

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690. (415) 863-5522.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Herbert M. Thomas, MD, MPH, Director of CME, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th Street, Los Angeles 90059. (213) 603-3183.

LLU: Loma Linda University
Contact: Varner J. Johns, Jr, MD, Associate Dean for Continuing Medical Education, Loma Linda University School of Medicine, Loma Linda 92354. (714) 796-7311, ext 2400.

PMC: Pacific Medical Center
Contact: Continuing Education, Pacific Medical Center, PO Box 7999, San Francisco 94120. (415) 563-4321, ext 2761.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Medical School Office Building, Suite X-365, Stanford 94305-6114. (415) 723-5594.

UCD: University of California, Davis
Contact: Ruth Feryok, Director, Office of Continuing Medical Education, University of California, Davis, School of Medicine, 2701 Stockton Boulevard, Sacramento 95817. (916) 453-5390.

UCI: University of California, Irvine
Contact: Melvin I. Marks, MD, Assistant Dean, University of California, Irvine, California College of Medicine, c/o UCI/CME Program, Memorial Medical Center, 2801 Atlantic Avenue, Long Beach 90801-1428. (213) 595-3811, or (714) 856-5414, UCI Extension.

UCLA: University of California, Los Angeles
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, PO Box 24902, UCLA, Los Angeles 90024. (213) 825-7241.

UCSD: University of California, San Diego
Contact: Office of Continuing Medical Education, University of California, San Diego, School of Medicine (M-017), La Jolla 92093. (619) 534-3713.

UCSF: University of California, San Francisco
Contact: Robert Maggio, Administrative Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 476-4251.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 1975 Zonal Ave, KAM314, Los Angeles 90033. (213) 224-7051.

(Continued on Page 108)

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CONTINUING MEDICAL EDUCATION

(Continued from Page 106)

ALLERGY

February 10-13—**Immunology and the Clinical Practice of Allergy.** UCSD. Wed-Sat. 20 hrs. $245. Contact: UCSD.

March 28-30—**Office and Hospital Based Clinical Nutrition for the Practitioner.** University of Washington at Maui, Hawaii. Mon-Wed. Contact: U/W School of Medicine, Div of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

ANESTHESIOLOGY

January 29-31—**26th Clinical Conference in Pediatric Anesthesiology.** Pediatric Anesthesiology Foundation at Los Angeles Airport Marriott Hotel. Fri-Sun. 15 hrs. $225. Contact: Wayne Herbert, MD, Childrens Hospital of Los Angeles, PO Box 54700, Los Angeles, CA 90054. (213) 669-2262.

January 31-February 5—**Biennial Western Conference on Anesthesiology: 1988 Clinical Update in Anesthesiology.** Toussaint Hospital Medical Education Program at Stouffer's Wailea Beach Resort, Maui, Hawaii. Sun-Fri. 22.5 hrs. $375. Contact: Murray G. Atnikov, c/o Box F110-63, Baline, WA 98230. (604) 874-5291.

March 13-18—**Anesthesiology 1988.** Anesthesiology Educational Foundation at Mammoth Lakes, Sierra Nevada Inn. Sun-Fri. Contact: Anesthesiology Educational Foundation, PO Box 24230, Los Angeles 90024.

March 19-20—**33rd Postgraduate Assembly.** Los Angeles Society of Anesthesiologists at Los Angeles Hilton Hotel. Sat-Sun. Contact: Laura Lee, Los Angeles Society of Anesthesiologists, PO Box 3465, Los Angeles, 90051-1465. (213) 483-1581 ext. 320.

May 15-20—**Hawaiian Seminar on Clinical Anesthesia.** California Society of Anesthesiologists at Sheraton Kauai Hotel, Poipu Beach, Kauai. Sun-Fri. 20 hrs. $325-375. Contact: California Society of Anesthesiologists, 1065 Hillsdale Blvd, #410, Foster City 94404. (415) 345-3020.

May 16-20—**5th International Symposium: Computing in Anesthesia and Intensive Care.** UCSD at US Grant Hotel, San Diego. Mon-Fri. 20 hrs. $300. Contact: UCSD.

June 16-19—**California Society of Anesthesiologists 1988 Annual Meeting** at Marriott Hotel, Anaheim. Thurs-Sun. 16 hrs. $150-225. Contact: California Society of Anesthesiologists, 1065 Hillsdale Blvd, #410, Foster City 94404. (415) 345-3020.

August 21-27—**Hawaiian Seminar on Clinical Anesthesia.** California Society of Anesthesiologists at Inter-Continental Hotel, Wailea, Maui. Sun-Sat. 20 hrs. $325/$375. Contact: CSA, 1065 E. Hilldale Blvd, Suite 410, Foster City 94404. (415) 345-3020.

October 16-21—**Hawaiian Seminar on Clinical Anesthesia.** California Society of Anesthesiologists at Westin Maui Hotel, Maui. Sun-Fri. 20 hrs. $325/$375. Contact: CSA, 1065 Hilldale Blvd, Suite 410, Foster City 94404. (415) 345-3020.

CANCER

February 4-6—**Third International Conference on Monoclonal Antibody Immunoconjugates for Cancer.** UCSD at Hotel Inter-Continental, San Diego. Thurs-Sat. 19 hrs. $310. Contact: UCSD.

February 25-27—**Second International Conference on Intracavitary Chemotherapy.** UCSD at US Grant Hotel, San Diego. Thurs-Sat. 18 hrs. $300. Contact: UCSD.

March 12—**Ultrasound in the Diagnosis and Management of Rectal Health.** Sutter Health at Sutter General Hospital, Sacramento. Sat. 6 hrs. $45. Contact: Sutter Health, CME Dept. 2020 I St, Suite D, Sacramento 95814. (916) 446-7681.

CARDIOLOGY

January 18-21—**Chest Imaging 1988.** San Diego Radiology and Research Education Foundation at the Hotel del Coronado, Coronado. Mon-Thurs. 22 hrs. $275. Contact: Dawne Ryals, Ryals and Associates, PO Box 920113, Norcross, GA 30092-0113. (404) 641-9773.

January 20-30—**Coronary Heart Disease: Current Concepts.** Medical Education Resources at Tropicana Hotel, Las Vegas, Fri-Sat. 11-13 hrs. $225-$292. Contact: MER, 5808 S. Rapp St. Suite 202, Littleton, CO 80120. (800) 421-3756.

January 22-24—**Advanced Cardiac Life Support,** CPR Seminars at Ralph K. Davies Medical Center. Fri-Sun. Contact: CPR Seminars, 833 Market St, Ste 421, San Francisco 94103. (415) 543-7282.

January 28-30—**Clinical Nuclear Cardiology.** ACC at Cedars-Sinai Medical Center, Los Angeles. Thurs-Sat. Contact: Mary Anne McInerny, ACC, 9111 Old Georgetown Rd, Bethesda, MD 20814. (301) 897-5400.

February 8-12—**3rd Annual Cardiovascular Conference at Hawaii.** ACC at Sheraton Royal Waikolua Hotel, Kona Coast, Hawaii. Contact: Mary Anne McInerny, American College of Cardiology, 9111 Old Georgetown Rd., Bethesda, MD 20814. (301) 897-5400.

February 10—**Cardiology Conference.** Enloe Memorial Hospital and Chico Community Hospital at The Esplanade Building, Enloe Hospital, Chico. Wed. 6 hrs. Contact: Bonnie Wells, Fifth Avenue and the Esplanade, Chico 95926. (916) 891-7375.

February 11-13—**Second Annual International Symposium: Clinical Strategies in Complex Valvular Heart Disease.** UCSD at US Grant Hotel, San Diego. Thurs-Sat. 16 hrs. $350. Contact: UCSD.

February 22-26—**Non-Invasive Diagnostic Techniques in Vascular Disease.** Scripps Clinic and Research Foundation at Sheraton Harbor Island Hotel,San Diego. Mon-Fri. 35 hrs. $550. Contact: Nomi Feldman, Conference Coordinator, 3770 Tansy St, San Diego, 92121. (619) 453-6222.

March 11-12—**Arrhythmias: Interpretation, Diagnosis and Management.** Medical Education Resources at Tropicana Hotel, Las Vegas, Nevada. Fri-Sat. 11-13 hrs. $225-$295. Contact: MER, 5808 S. Rapp St., Suite 202, Littleton, CO 80120. (800) 421-3756.

March 21-23—**New Directions in Cardiac Rehabilitation.** ACC & Stanford University School of Medicine at Stanford. Mon-Wed. Contact: Registration Secretary EP Dept., ACC, Bethesda, MD (301) 897-5400.

March 25-27—**Coronary Heart Disease: Current Concepts.** Medical Education Resources at Inter-Continental Hotel, Maui, Hawaii. Fri-Sun. 11-13 hrs. $225-$295. Contact: MER, 5808 S. Rapp St., Suite 202, Littleton, CO 80120. (800) 421-3756.

April 15-17—**Coronary Artery Disease: A Commemorative Symposium—75 Years Since Anitschkow and Herrick.** UCSF. Contact: UCSF.

April 18-27—**Cardiology for the Consultant.** Scripps Clinic and Research Foundation at the Inn at Rancho Santa Fe, Rancho Santa Fe. Mon-Wed. 40 hrs. $900. Contact: Bonny Mower, 10666 N. Torrey Pines Road, La Jolla, 92037. (619) 457-8556.

May 7—**Third Annual Cardiology Symposium.** Sutter Health at Sacramento Inn, Sacramento. Sat. 6 hrs. Contact: Sutter Health, CME Dept. 2020 I St, Suite D, Sacramento 95814. (916) 446-7681.

May 13-14—**Coronary Heart Disease: Current Concepts.** Medical Education Resources at Hilton Hotel, San Francisco. Wed-Thur. 11-13 hrs. $225-$295. Contact: MER, 5808 S. Rapp St., Suite 202, Littleton, CO 80120. (800) 421-3756.

May 19-20—**Cardiology for the Non-Cardiologist.** UCI. Thurs-Fri. Contact: UCI.

June 6-8—**Advanced Echocardiography & Doppler Ultrasound 1988.** American College of Cardiology at Sheraton Harbor Island, San Diego. Mon-Wed. Contact: Registration Secretary, EP Dept. ACC, 9111 Old Georgetown Road, Bethesda, MD 20814.

June 30-July 2—**Consultative Cardiology: Update in Diagnostic and Therapeutic Techniques.** ACC, Orange Coast Heart Institute and Hoag Memorial Hospital at Westin South Coast Plaza, Costa Mesa. Thur-Sat. Contact: Registration Secretary, EP Dept., ACC, 9111 Old Georgetown Road, Bethesda, MD 20814.

DERMATOLOGY

January 22-24—**Practical Dermatology and Dermatologic Office Procedures for the Primary Care Physician.** UCSD at San Diego Princess, San Diego. Fri-Sun. 20 hrs. $375. Contact J. SHiller, PO Box 84296, San Diego, 92138. (619) 223-2997.

August 12-14—**Dermatologic Surgery: State of the Art 1988.** Stanford University at Monterey Sheraton, Monterey. Fri-Sun. Contact: Paul H. Jacobs, MD, Dept. of Dermatology, UMC Stanford, 94305. (415) 723-6105.

EMERGENCY MEDICINE

March 6-11—**9th Annual Mammoth Mt. Emergency Medicine Ski Conference.** UCI and Orange County Emergency Dept. Nurses Assoc. at Mammoth Lakes. Sun-Fri. 20 hrs. $350. Contact: CME Travel Services, 1615 S. Mission Road, Suite 3, Fallbrook 92028.

(Continued on Page 112)

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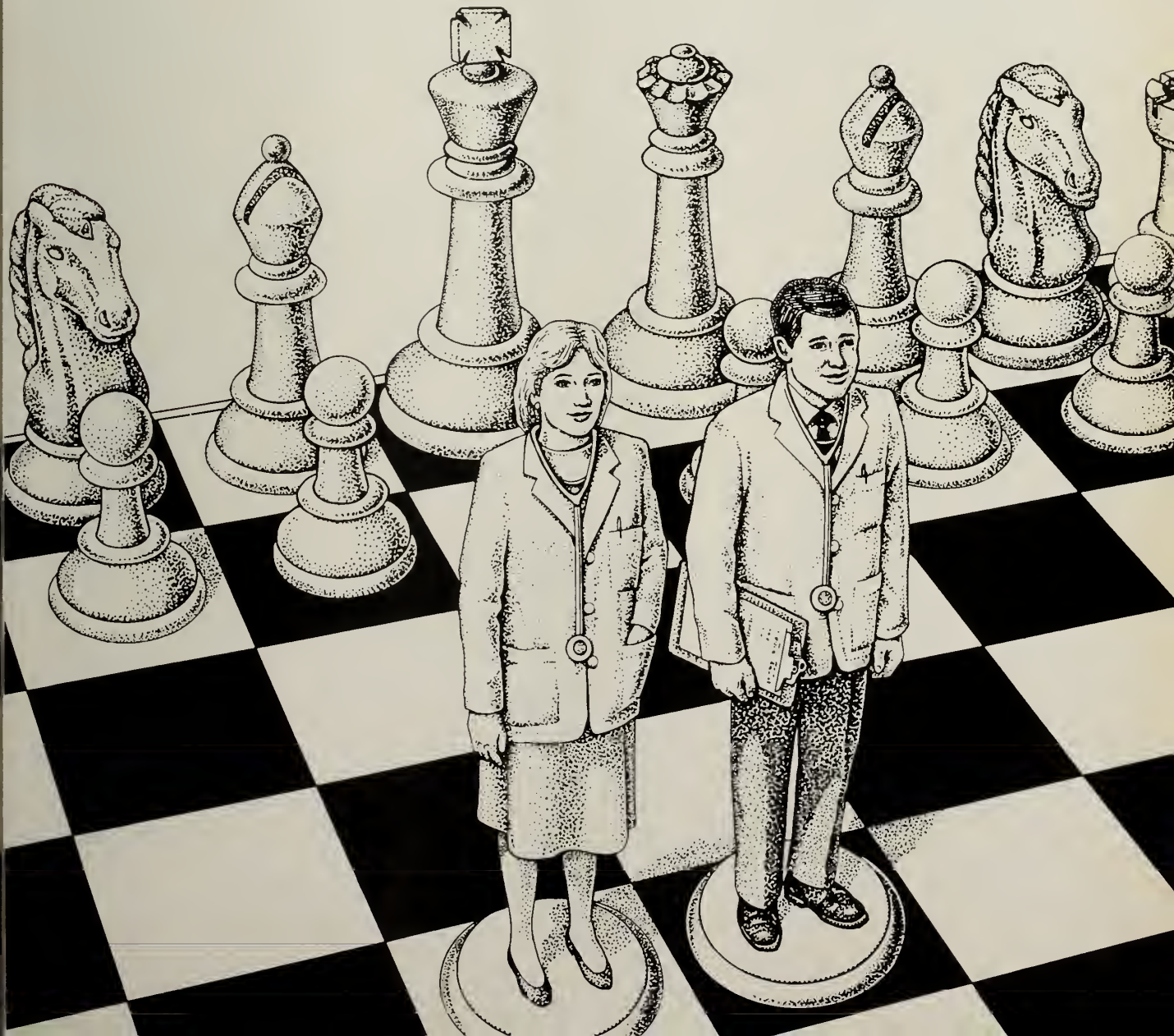

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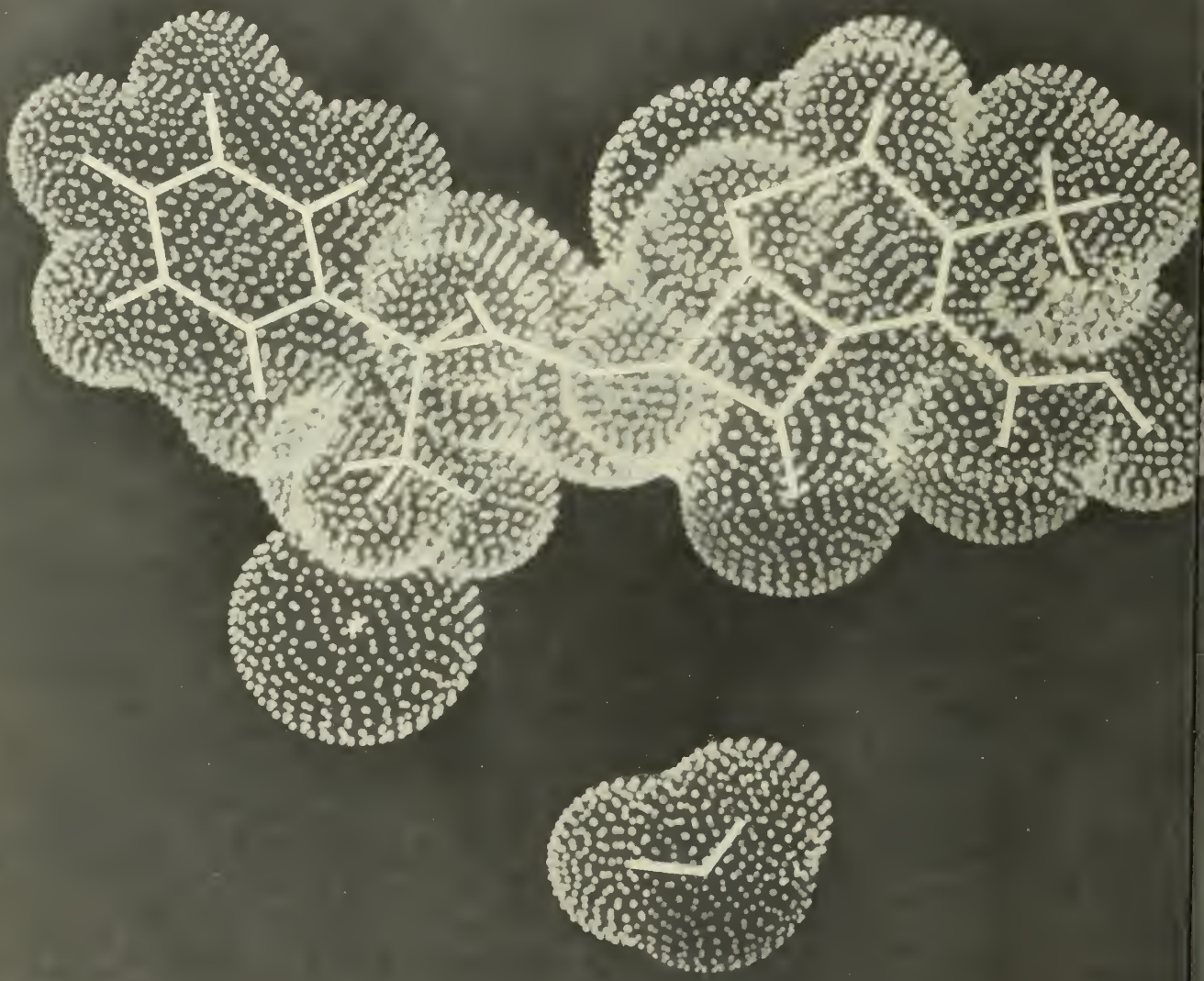

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Skin and skin structure infections caused by susceptible strains of *Staphylococcus aureus* and/or β-hemolytic streptococci.

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Warnings: KEFTAB SHOULD BE ADMINISTERED CAUTIOUSLY TO PENICILLIN-SENSITIVE PATIENTS. PENICILLINS AND CEPHALOSPORINS SHOW PARTIAL CROSS-ALLERGENICITY. POSSIBLE REACTIONS INCLUDE ANAPHYLAXIS.

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Precautions:

- Discontinue Keftab in the event of allergic reactions to it.
- Prolonged use may result in overgrowth of nonsusceptible organisms.
- Positive direct Coombs' tests have been reported during treatment with cephalosporins.
- Keftab should be administered cautiously in the presence of markedly impaired renal function. Although dosage adjustments in moderate to severe renal impairment are usually not required, careful clinical observation and laboratory studies should be made.
- Broad-spectrum antibiotics should be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis.
- Safety and effectiveness have not been determined in pregnancy and lactation. Cephalexin is excreted in mother's milk. Exercise caution in prescribing Keftab for these patients.
- Safety and effectiveness in children have not been established.

Adverse Reactions:

- *Gastrointestinal*, including diarrhea and, rarely, nausea and vomiting. Transient hepatitis and cholestatic jaundice have been reported rarely.
- *Hypersensitivity* in the form of rash, urticaria, angioedema, and, rarely, erythema multiforme, Stevens-Johnson syndrome, or toxic epidermal necrolysis.
- *Anaphylaxis* has been reported.
- *Other reactions* have included genital/anal pruritus, genital moniliasis, vaginitis/vaginal discharge, dizziness, fatigue, headache, eosinophilia, neutropenia, and thrombocytopenia; reversible interstitial nephritis has been reported rarely.
- Cephalosporins have been implicated in triggering seizures, particularly in patients with renal impairment.
- *Abnormalities in laboratory test results* included slight elevations in aspartate aminotransferase (AST, SGOT) and alanine aminotransferase (ALT, SGPT). False-positive reactions for glucose in the urine may occur with Benedict's or Fehling's solution and Clinitest® tablets but not with Tes-Tape® (Glucose Enzymatic Test Strip, USP, Lilly).

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CONTINUING MEDICAL EDUCATION

(Continued from Page 108)

March 23-25—**Advances in Emergency Medicine.** UCSF at Holiday Inn Union Square, San Francisco. Wed-Fri. $300. Contact: UCSF.

March 25-26—**Advances in Emergency Medicine: Toxicology and Infectious Diseases.** UCLA at San Diego Hilton, Mission Bay. Fri-Sat. 9 hrs. Contact: UCLA.

May 11-15—**Tenth Annual Wound Management Workshop.** UCSD at San Diego Hilton Beach and Tennis Resort. Wed-Sun. 19 hrs. Contact: Edith S. Bookstein/WMW, PO Box 1386, La Jolla 92038. (619) 454-3212.

INTERNAL MEDICINE

December 20-24—**Immunology, Rheumatology and Allergy.** Symposium Maui at Royal Lahaina Resort, Maui. Sun-Thurs. 18 hrs. $395. Contact: Symposium Maui, Inc., PO Box 10185, Lahaina, HI 96761. (808) 879-8182.

January 1-4—**Specialties and Primary Practice.** Symposium Maui at Royal Lahaina Resort, Maui. Fri-Mon. 13.5 hrs. $295. Contact: Symposium Maui, Inc., PO Box 10185, Lahaina, HI 96761. (808) 879-8182.

January 19-23—**Intensive Course in Geriatric Medicine and Board Review.** UCLA at Beverly Hilton, Beverly Hills. Tues-Sat. 40 hrs. Contact: UCLA.

February 1-12—**21st Annual Recent Advances in Neurology.** UCSF at Fairmont Hotel, San Francisco. Wed-Fri. 15.5 hrs. $335. Contact: UCSF.

February 7-12—**General Internal Medicine: Concepts and Controversies.** UCSF at Hyatt Lake Tahoe, Incline Village. Sun-Fri. 18.5 hrs. $365. Contact: UCSF.

February 10-12—**21st Annual Recent Advances in Neurology.** UCSF. Wed-Fri. 15.5 hrs. $335. Contact: UCSF.

February 12-13—**Infectious Disease.** UCD at Sheraton Sunrise, Sacramento. Fri-Sat. Contact: UCD.

February 13-14—**Skills Workshop: Flexible Sigmoidoscopy and Colposcopy.** UCI at Sheraton Newport, Newport Beach. Sat-Sun. 16 hrs. $250 for both. Contact: UCI.

February 15-17—**Clinical Hematology and Oncology: 1988.** Scripps Clinic and Research Foundation at San Diego Princess Resort. Mon-Wed. Contact: Bonny Mower, Box 400s, Scripps Clinic and Research Foundation, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 457-8556.

February 19-21—**Update on Gastroenterology: Diagnosis and Therapy.** The Center for Health Education at the Newporter Resort, Newport Beach. Fri-Sun. Contact: The Center for Continuing Education, 2081 Atlantic Ave, PO Box 1428, Long Beach 90801-1428.

February 21-26—**Emergencies in Internal Medicine: 11th Annual UCD Winter Conference.** UCD at Hyatt Lake Tahoe, Incline Village, Nevada. Sun-Fri. 23 hrs. $395. Contact: UCD.

March 4-5—**Gastrointestinal Endoscopy 1988.** Southern California Society for Gastrointestinal Endoscopy at Century Plaza Hotel, Los Angeles. Fri-Sat. Contact: David S. Cantor, MD, 50 Alessandro, Ste 410, Pasadena 91105. (818) 793-7114.

March 9-10—**Advances in Endocrinology and Metabolism.** UCSF at Holiday Inn Union Square, San Francisco. Wed-Thurs. $250/$150. Contact: UCSF.

March 11-17—**Internal Medicine 1988: A Comprehensive Review.** Sharp Memorial Hospital at Hotel Del Coronado, Coronado. Fri-Thurs. 54 hrs. $495. Contact: Jackie Shiller, Continuing Medical Education Associates, PO Box 84296, San Diego 92138. (619) 223-2997.

March 16-19—**Frontiers in Clinical Rheumatology.** UCD at Clarion Inn, Napa. Wed-Sat. Contact: UCD.

May 23-27—**Advances in Internal Medicine.** UCSF at Sheraton-Palace Hotel, San Franicsco. Mon-Fri. 32 hrs. $440. Contact: UCSF.

June 6-10—**Advances in Internal Medicine.** UCSF at Cole Hall. 32 hrs. $440. Contact: UCSF.

OB/GYN

January 18-22—**19th Review Course in Obstetrics and Gynecology.** USC at Pasadena Hilton Hotel. Mon-Fri. 35.5 hrs. $545. Contact: USC.

January 31-February 4—**OB/GYN Update 1988.** UCD at Hyatt Lake Tahoe, Incline Village, NV. Sun-Thur. Contact: UCD.

February 7-11—**16th Obstetric Anesthesia Conference.** Ohio State University at Sheraton Waikiki Hotel, Waikiki. Sun-Thurs. Contact: Ohio State University, 410 W 10th Ave, Columbus, Ohio 43210. (614) 293-8487.

February 11-14—**43rd Annual Postgraduate Assembly.** OB-GYN Assembly of Southern California at Beverly Hilton Hotel, Beverly Hills. Thurs-Sun. 28 hrs. Contact: Director of Medical Education, OB-GYN Assembly of California, 5820 Wilshire Blvd, #500, Los Angeles 90036. (213) 937-5514.

February 19-21—**Office Gynecology for the Primary Care Physician.** San Diego State University at Hyatt Islandia, San Diego. Fri-Sun. 18 hrs. $295. Contact: J. Shiller, Continuing Medical Education Associates, PO Box 84296, San Diego, 92138. (619) 223-2997.

March 16-19—**5th Annual Horizon in Reproductive Health Medical Conference.** UCSD at Hotel del Coronado, Coronado. Wed-Sat. Contact: Mary Fessel, 2100 5th Ave., San Diego, 92101. (619) 231-6760.

March 25-26—**GYN/Urology.** UCI at Hilton Riviera, Palm Springs. Fri-Sat. Contact: UCI.

April 21-23—**10th Annual Orange County OB/GYN Congress.** Orange County Obstetrical and Gynecological Society at Westin Hotel, South Coast Plaza, Costa Mesa. Thur-Sat. 15 hrs. $300. Contact: Paula Rogers, P.O. Box 1297, Orange 92668. (714) 978-1260.

June 30-July 3—**6th Annual Controversies in Obstetrics & Gynecology.** Center for Health Education at Mauna Kea Beach Hotel, Hawaii. Thur-Sun. Contact: The Center for Health Education, 2081 Atlantic Ave., P.O. Box 1428, Long Beach, 90801-1428. (213) 595-3811.

OPHTHALMOLOGY

January 31-February 4—**Tahoe Vitreoretinal Symposium.** UCD Retina Faculty at Granlibakken Ski Resort, Lake Tahoe. Sun-Thur. $360. Contact: Richard A. Murray, MD, 2701 "I" Street, Sacramento, CA 95816. (916) 442-4975.

March 18—**Visions in Ophthalmology '88.** Scripps Memorial Hospital at La Jolla Marriott, San Diego. Fri. 6 hrs. $75. Contact: Nomi Feldman, Conference Coordinator, 3770 Tansy St, San Diego 92121. (619) 453-6222.

PEDIATRICS

January 16—**Pediatric Cardiology for the Primary Physician.** Children's Hospital Oakland at Merritt Peralta Health Education Center, Oakland. Sat. 6 hrs. Contact: Kim Leadon, Continuing Medical Education, Children's Hospital Oakland, 747-52nd St, Oakland 94609. (415) 428-3021.

January 24-27—**13th Annual Winter Ski and Study Symposium.** California Chapters 1 & American Academy of Pediatrics at Caesars Tahoe Hotel, Lake Tahoe. Sun-Wed. $250. Contact: American Academy of Pediatrics, Chapter 2, P.O. Box 2134, Inglewood 90305. (213) 757-1198.

January 29-31—**26th Clinical Conference in Pediatric Anesthesiology.** Pediatric Anesthesiology Foundation at Los Angeles Airport Marriott Hotel. Fri-Sun. 15 hrs. $225. Contact: Wayne Herbert, MD, Childrens Hospital of Los Angeles, PO Box 54700, Los Angeles 90054. (213) 669-2262.

February 4-6—**Current Concepts in Pediatric Medicine—1988.** Childrens Hospital and Health Center, San Diego at Holiday Inn, Embarcadero, San Diego. Thurs-Sat. Contact: Children's Hospital San Diego. 8001 Frost St, San Diego 92123. (619) 576-1700.

February 20-27—**Pediatric Emergencies.** Scripps Memorial Hospital, Encinitas and American Institute of Postgraduate Education at Royal Lahaina Resort, Maui. One week. 21 hrs. $395. Contact: Edith S. Bookstein/AIPE, PO Box 2586, La Jolla 92038. (619) 454-3212.

February 22-24—**Pediatrics Update 1988.** San Diego State University at Hyatt Islandia, San Diego. Mon-Wed. 18 hrs. $295. Contact: J. Shiller, POBox 84296, San Diego 92138. (619) 223-2997.

March 12—**Behavioral/Development Pediatrics Symposium: Stress, Vulnerability and Child Health.** UCSF. Sat. 6.5 hrs. Contact: UCSF.

March 18-19—**Hematology: Neonatal, Pediatric & AIDS Related Issues.** Children's Hospital Oakland at Berkeley Marina Marriott Hotel, Fri-Sat. 11 hrs. Contact: Kim Leadon, CME Dept. Children's Hospital, 747 52nd Street, Oakland 94609. (415) 428-3021.

April 8-9—**UCD Annual Pediatrics Program.** UCD at Red Lion Motor Inn, Sacramento. Fri-Sat. Contact: UCD.

(Continued on Page 114)

SPECIAL ISSUES

AIDS—A Global Perspective

The short and remarkable history of AIDS epidemiology began in 1981 with the description of the clinical syndrome in California and New York. In the 6 years that have followed, intensive epidemiologic studies have defined the mode of spread of AIDS and laid the foundation for current control efforts. Serosurveys and retrospective clinical studies have been used to trace the temporal origins of the pandemic prior to 1981, while prospective studies and an increasingly comprehensive worldwide surveillance system have provided more accurate data for the years following 1981. AIDS cases have now been reported and investigated throughout the world.

This issue, from the Special Programme on AIDS of the World Health Organization, considers the methods and limitations of AIDS case reporting and HIV serologic studies, summarizes modes of HIV transmission, defines geographic patterns of spread, and examines the epidemiology of HIV infections by continent.

—Jonathan M. Mann, MD
Director, Special Programme on AIDS
World Health Organization, Geneva

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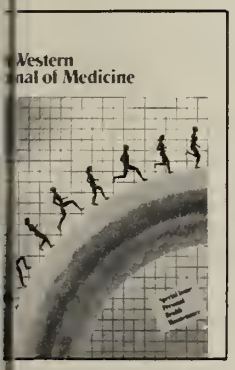

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The goal of this special issue is to provide an authoritative, current guide to disease prevention and health promotion. The contributors are distinguished experts in public health, epidemiology and clinical medicine.

—John H. Holbrook, MD

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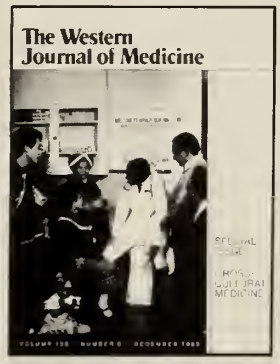

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—Malcolm S. M. Watts, MD

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CONTINUING MEDICAL EDUCATION

(Continued from Page 112)

April 29-30—**21st Annual Advances and Controversies in Clinical Pediatrics.** UCSF at Mark Hopkins Hotel, San Francisco. Fri-Sat. 16.5 hrs. Contact: UCSF.

October 22-29—**13th Annual Pediatrics for the Practitioner: A Pediatric Symposium.** Center for Health Education at Mauna Kea Beach Hotel, Hawaii. One week. Contact: The Center for Health Education, PO Box 1428, Long Beach 90801-1428.

PSYCHIATRY

January 21-24—**Health Science Response to Child Maltreatment—1988.** Children's Hospital and Health Center ar Hanalei Hotel, San Diego. Thurs-Sun. 17 hrs. Contact: Children's Hospital and Health Center, 8001 Frost St, San Diego 92123. (619) 576-1700.

January 24-29—**14th Annual Midwinter Program for Psychiatrists—Special Focus on Aquired Immune Deficiency Syndrome (AIDS).** UCD at Hyatt Lake Tahoe, Nevada. Sun-Fri. 25 hrs. Contact: UCD.

January 28—**Claudia Black: Loss of Childhood—And Recovery in Adulthood.** UCSD at Monterey Conference Center, Monterey. Thurs. Contact: Nomi Feldman, Conference Coordinator, 3770 Tansy St, San Diego 92121. (619) 453-6222.

February 6-7—**Intensive Short-Term Dynamic Psychotherapy With Highly Resistant Patients.** UCSD at Sheraton Harbor Island Hotel, San Diego. Sat-Sun. $275. Contact: Nomi Feldman, Conference Coordinator, 3770 Tansy St, San Diego 92121. (619) 453-6222.

March 27-31—**Adapting to Social Change, Therapy, Technology and Services.** American Orthopsychiatric Association at Hilton Square, San Francisco. Sun-Thurs. Contact: ORTHO, 19 W 44th St, #1616, New York, NY 10036. (212) 354-5770.

April 15-16—**3rd Annual Work and Mental Health Symposium.** UCSF at Holiday Inn Union Square, San Francisco. Fri-Sat. 12 hrs. $200. Contact: UCSF.

April 23-24—**The Cutting Edge 1988: Innovations in Psychotherapy: Helping Individuals and Couples to Change.** UCSD at Hotel Del Coronado, San Diego. Sat-Sun. 13 hrs. $275. Contact: UCSD.

May 23-24—**Child Abuse.** UCD at Holiday Inn Holidome, Sacramento. Mon-Tue. Contact: UCD.

RADIOLOGY

January 21-23—**Duplex Imaging.** UCSD at Inter-Continental Hotel, San Diego. Thurs-Sat. 18 hrs. $375. Contact: UCSD.

January 24-31—**Radiology for Emergency & Primary Care Physicians.** American Institute of Postgraduate Education and Scripps Memorial Hospital, Encinitas at Kona Surf Resort, Kona, Hawaii. One Week. 21 hrs. $395. Contact: Edith S. Bookstein/AIPE, PO Box 3586, La Jolla 92038. (619) 454-3212.

January 25-28—**Selected Topics in Nuclear Radiology—1988.** Dept. of Radiology, UCSD at Hotel Del Coronado, San Diego. Mon-Thur. 18.75 hrs. $375. Contact: Mary J. Ryals, P.O. Box 920113, Norcross, GA 30092-0113. (404) 641-9773.

January 29-31—**Fortieth Annual Midwinter Oncology Conference.** Los Angeles Radiological Society at Century Plaza Hotel, Los Angeles. Fri-Sun. 20hrs. $250. Contact: Los Angeles Radiological Society-MWOC, PO Box 91215, Los Angeles 90009. (213) 642-0921.

February 2-6—**14th Annual Post Conference Seminar.** Los Angeles Radiological Society at Century Plaza Hotel, Los Angeles. Tues-Sat. 18 hrs. $375. Contact: Los Angeles Radiological Society-MWRC, PO Box 91215, Los Angeles 90009. (213) 642-0921.

February 21-24—**7th Annual UCSD Imaging & Intervention Conference.** UCSD, Dept. of Radiology at Hotel Inter-Continental, San Diego. Sun-Wed. 25 hrs. $400. Contact: Mary J. Ryals, P.O. Box 920113, Norcross, GA 30092-0113. (404) 641-9773.

March 7-11—**Neuroradiology Update.** UCSD at Hotel Del Coronado, San Diego, Mon-Fri. Up to 28 hrs. Contact: Mary J. Ryals, P.O. Box 920113, Norcross, GA 30092-0113. (404) 641-9773.

March 9-11—**8th Annual Current Approaches to Radiation, Oncology, Biology and Physics.** UCSF at Hotel Nikko, San Francisco. Wed-Fri. 18 hrs. Contact: The Crest Organization, Outside CA (800) 222-8882; Inside CA (415) 595-2704.

April 10-15—**8th Annual San Diego Resident's Radiology Review Course.** UCSD at Town & Country Hotel, San Diego. Sun-Fri. Contact: Mary J. Ryals, P.O. Box 920113, Norcross, GA 30092-0113. (404) 641-9773.

SPORTS MEDICINE

January 17-22—**Sports Medicine: 1988.** UCD at Hyatt Lake Tahoe, Nevada. Sun-Fri. 28 hrs. $435. Contact: UCD.

SURGERY

February 20-21—**Advances in Sclerotherapy and Advances in Surgical and Medical Treatment of Venous Diseases.** Scripps Clinic and Research Foundation at Sheraton Grand Hotel, San Diego. Sat-Sun. 9 hrs. $125. Contact: Helane Fronek, MD, 3051 Cranbrook Ct, La Jolla 92037

March 3-6—**Surgical Forum.** Society of Graduate Surgeons of the Los Angeles County/University of Southern California Medical Center at the Biltmore Hotel, Los Angeles. Thurs-Sun. 25 hrs. $400. Contact: Society of Graduate Surgeons, 5820 Wilshire Blvd, Suite 500, Los Angeles 90036.

March 14-17—**Controversies in General and Vascular Surgery.** UCLA at Palm Springs Spa Hotel, Palm Springs. Mon-Thurs. Contact: UCLA.

March 17-20—**The International Symposium on Hair Replacement Surgery.** American Academy of Facial Plastic and Reconstructive Surgery at Four Seasons Hotel, Los Angeles. Thurs-Sun. 30 hrs. Contact: AAFPRS Foundation, 1101 Vermont Ave, NW, Suite 404, Washington, DC, 20005.

April 14-16—**Postgraduate Course in General Surgery.** UCSF. Thur-Sat. Contact: UCSF.

April 15-17—**The 5th Annual San Diego Meeting on Arthroscopic Surgery of the Shoulder.** Tri-City Orthopaedic & Sports Physical Therapy Medical Group, Inc. at La Jolla Marriott Hotel, La Jolla. Fri-Sun. Contact: James C. Esch, MD, 3905 Waring Rd, Oceanside 92056. (619) 724-9000.

OF INTEREST TO ALL PHYSICIANS

January 1-4—**Specialties & Primary Practice.** Symposium Maui, Inc. at Royal Lahaina Resort, Maui. Fri-Mon. 13.5 hrs. $295. Contact: Symposium Maui, Inc. P.O. Box 10185, Maui, Hawaii. (808) 879-8182.

January 20—**Managing and Controlling Asbestos Contamination/Exposure.** USC Institute of Safety and Systems Management at Los Angeles. Wed. $160. Contact: USC.

January 21-22—**Transportation of Hazardous Materials/Waste.** USC. Thur-Fri. $265. Contact: USC.

January 22-23—**5th Annual Reider Laser Symposium: Urology.** Center for Health Education at Hyatt Regency, Long Beach. Fri-Sat. 12 hrs. Contact: CHE, PO Box 1428, Long Beach 90801-1428. (213) 595-3811.

January 25-29—**Hazardous Materials: Handling and Disposal.** USC. Mon-Fri. $735. Contact: USC.

February 1—**Hazardous Waste Management of Small Generators.** USC. Mon. 1 hr. $160. Contact: USC.

February 2-4—**11th Annual: Neurology for Non-Neurologists.** UCSD and Neurology for Non-Neurologists Foundation at Holiday Inn Embarcadero, San Diego. Tues-Thurs. 21 hrs. $395. Contact: Edith S. Bookstein/NNN, PO Box 3586, La Jolla 92038. (619) 454-3212.

February 3-5—**Clinical Laboratory Molecular Analysis: Future Perspectives.** Scripps Clinic and Research Foundation at San Diego Princess Resort. Wed-Fri. 24 hrs. Contact: Bonny Mower, Box 400s, Scripps Clinic and Research Foundation, 10666 N Torrey Pines, Rd, La Jolla 92037. (619) 457-8556.

February 4-6—**Evaluating Recovery Outcomes-National Conference.** UCSD at Bahia Hotel, Mission Bay. Thurs-Sat. 15 hrs. $300. Contact: UCSD.

February 8-12—**Family Practice Refresher Course.** UCI at Sheraton Newport, Newport Beach. Mon-Fri. 44.5 hrs. $575. Contact: UCI.

February 8-13—**The UCI Family Practice Refresher Course.** The Center for Health Education at Newport Sheraton, Newport Beach. Mon-Sat. Contact: The Center for Health Education, 2081 Atlantic Ave., P.O. Box 1428, Long Beach, 90801-1428. (213) 595-3811.

February 11-12—**Back Injury Prevention.** USC. Thur-Fri. $280. Contact: USC.

(Continued on Page 118)

DON'T OVERLOOK THE EYES WHEN TREATING ALLERGIES

More than 8 out of 10 patients who present with allergic rhinitis may suffer from concurrent allergic ocular signs and symptoms —itchy, scratchy eyes, erythema and edema, tearing, irritation—according to two recent studies.[1,2]

What's worse is that many patients don't mention their ocular symptoms when reporting allergic rhinitis unless specifically asked.

So look for the overlapping clinical symptoms and then confidently treat allergic ocular disorders* with OPTICROM. It has a proven clinical record of efficacy with freedom from serious side effects or ocular toxicity.

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Reference 1,2. Data on file, Fisons Corporation.
Independent Studies by DTW Market Research Group July 1985

*See below for listing of certain allergic ocular disorders

INDICATIONS AND USAGE: OPTICROM is indicated in the treatment of certain allergic ocular disorders referred to by the terms vernal keratoconjunctivitis, vernal conjunctivitis, giant papillary conjunctivitis, vernal keratitis, and allergic keratoconjunctivitis. The etiologic factors are unknown, but common airborne allergens and contact lenses have been implicated.[1]

Symptomatic response to therapy (decreased itching, tearing, redness, and discharge) is usually evident within a few days, but longer treatment for up to six weeks is sometimes required. Once symptomatic improvement has been established, therapy should be continued for as long as needed to sustain improvement.

If required, corticosteroids may be used concomitantly with OPTICROM.

Users of soft (hydrophilic) contact lenses should refrain from wearing lenses while under treatment with OPTICROM (see **Contraindications**). Wear can be resumed within a few hours after discontinuation of the drug.

CONTRAINDICATIONS: OPTICROM is contraindicated in those patients who have shown hypersensitivity to cromolyn sodium or to any of the other ingredients.

As with all ophthalmic preparations containing benzalkonium chloride, patients are advised not to wear soft contact lenses during treatment with OPTICROM.

PRECAUTIONS: General: Patients may experience a transient stinging or burning sensation following application of OPTICROM.

The recommended frequency of administration should not be exceeded. The dose for adults and children is 1-2 drops in each eye 4-6 times a day at regular intervals.

Carcinogenesis, Mutagenesis, and Impairment of Fertility: Long term studies in mice (12 months intraperitoneal treatment followed by six months observation), hamsters (12 months intraperitoneal treatment followed by 12 months observation), and rats (18 months subcutaneous treatment) showed no neoplastic effect of cromolyn sodium.

No evidence of chromosomal damage or cytotoxicity was obtained in various mutagenesis studies.

No evidence of impaired fertility was shown in laboratory animal reproduction studies.

Pregnancy: Pregnancy Category B. Reproduction studies with cromolyn sodium administered parenterally to pregnant mice, rats and rabbits in doses up to 338 times the human clinical doses produced no evidence of fetal malformations. Adverse fetal effects (increased resorption and decreased fetal weight) were noted only at the very high parenteral doses that produced maternal toxicity. There are, however, no adequate and well controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when OPTICROM is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in children below the age of 4 years have not been established.

ADVERSE REACTIONS: The most frequently reported adverse reaction attributed to the use of OPTICROM, on the basis of reoccurrence following readministration, is transient ocular stinging or burning upon instillation.

The following adverse reactions have been reported as infrequent events. It is unclear whether they are attributable to the drug: conjunctival injection, watery eyes, itchy eyes, dryness around the eye, puffy eyes, eye irritation, styes.

CAUTION: Federal law prohibits dispensing without prescription.

REFERENCE: 1. Allansmith MR, Abelson MB. Ocular Allergies. In: *The Cornea*, ed. by G. Smolin, RA Thoft, Little, Brown and Co., Boston/Toronto, 1983: 231-43.

See package insert for full prescribing information.

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ARIZONA-BASED PHYSICIAN recruiting firm has opportunities coast-to-coast. "Quality Physicians for Quality Clients since 1972." Call (602) 990-8080; or send CV to Mitchell & Associates, Inc, PO Box 1804, Scottsdale, AZ 85252.

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SOUTH CENTRAL WYOMING. Immediate practice opportunity for BC/BE Urologist. Well-equipped JCAH hospital for a service area of approximately 20,000 population. No state or city income tax. Relocation incentives. Superior hunting, fishing, camping, snowmobiling. Three hours to Colorado ski area, five hours to Jackson Hole. One and one-half hours to the mountains. If interested, please send CV and references to D. Abels, DO, Chairman, Recruiting Committee or Richard Mills, Executive Director, Memorial Hospital of Carbon County, Rawlins, WY 82301; (307) 324-2221.

PHYSICIANS WANTED

NEUROLOGIST. Visalia Medical Clinic, Inc, a 37 physician multispecialty group, is searching for a Neurologist to enter an active practice. Located in the San Joaquin Valley in California and serving a market area of approximately 350,000. Excellent hospital services and facilities. BC/BE. Compensation is incentive oriented with rapid advancement to full partnership. Excellent fringe benefits. Please respond to John G. Heinsohn, Administrator, 5400 W. Hillsdale, Visalia, CA 93291; (209) 733-5222.

DERMATOLOGIST. Visalia Medical Clinic has an opening for a BC/BE Dermatologist now staffed by one physician who has been with the Clinic for 15 years. Located in the San Joaquin Valley in central California and population approximately 350,000. Progressive city of 62,000, near national parks and the ocean. Compensation is incentive oriented with advancement to full partnership after one year. Excellent fringe benefits. If interested, CV to John G. Heinsohn, Administrator, 5400 W. Hillsdale, Visalia, CA 93291; (209) 733-5222.

NEUROSURGERY. Visalia Medical Clinic has an opening for a BC/BE Neurological Surgeon to enter an immediate and active practice. Located in the San Joaquin Valley of California, serving a market area of approximately 350,000 citizens. Two Neurosurgeons presently serving this area. Excellent hospital services and facilities. Must be BC/BE. Compensation is incentive oriented with advancement to full partnership after one year. Excellent fringe benefits. John G. Heinsohn, Administrator, 5400 W. Hillsdale, Visalia, CA 93291; (209) 733-5222.

CALIFORNIA. Emergency Medicine Faculty Positions. Immediate opportunities available for career-oriented Emergency Physicians who possess excellent clinical and teaching skills to join the faculty of Emergency Medicine department. BC in Family Practice, Internal Medicine, Surgery, and/or BE in Emergency Medicine. Our facility, located in southern California, averages 38,000 Emergency department visits per year, is a level II trauma center, regional burn center and neonatology intensive care center. These positions require a teaching commitment in a university-affiliated Family Practice training program. We offer a competitive remuneration package to include salary, malpractice insurance, time off, and flexible scheduling. Send CV to Empire Medical Group, PO Box 3571, San Bernardino, CA 92413.

PHYSICIANS WANTED

BEAUTIFUL COLORADO—Family Practice, Internal Medicine, and Occupational Physicians. Send CV to D. A. Franklin, MD, Medical Director, HealthWatch Medical Centers, 3400 Industrial Lane, Ste A, Broomfield, CO 80020.

INTERNIST BC/BE to assume busy established practice. Share call with three other Internists. Excellent hospital and family oriented community. University affiliation possible. Send CV to Search Committee, PO Box 1564, Redlands, CA 92373.

BROOKINGS, OREGON. Evening and weekend clinic. Family practice or emergency experience preferred. $35 per hour. Send CV to Art B. Wong, MD, FACEP, Emergency Physicians' Medical Group, 1 Maritime Plaza, Ste 710, San Francisco, CA 94111.

FAMILY PRACTICE PHYSICIAN. Southern California, Los Angeles suburb. BC/BE FP desired for group practice. Join five residency trained FPs in comprehensive practice. OB optional. Excellent hospital and support services. Salary, production, and benefits commensurate with experience. Malpractice paid. Send CV or call Mr Ed Myatt, Executive Director, Northridge Community Medical Group, 8330 Reseda Blvd., Northridge, CA 91324; (818) 886-1376.

GASTROENTEROLOGIST BC/BE to be a second Gastroenterologist in a 36 physician multispecialty clinic. Guaranteed salary and immediate full participation in incentive program. Excellent benefit package with excellent recreational, cultural, and educational opportunities. Send CV to Search Committee, Walla Walla Clinic, 55 West Tietan, Walla Walla, WA 99362.

OB/GYN. Multispecialty group in northwest Washington desires second Obstetrician. Excellent practice opportunity, full range of benefits, early partnership status, all practice costs paid. For more information contact Shane Spray, Administrator, 1400 E. Kincaid, Mount Vernon, WA 98273; (206) 428-2524.

NEW MEXICO. BC/BE Primary Care Physician for 500-bed psychiatric/geriatric hospital. Exciting programs in an exciting location, with superb climate, recreational and cultural benefits. Base salary $70,017 plus optional on-call salary supplement to $10,000. Fringe benefits are 21%, including paid malpractice and license fees, 2.5% per year retirement. Contact Philip Taulbee, MD, Medical Director, Las Vegas Medical Center, Box 1388, Las Vegas, NM 87701; (505) 425-6711.

OREGON—FAMILY PRACTITIONERS, INTERNISTS, PEDIATRICIANS. Private practice opportunities are immediately available in beautiful northwest Oregon. Call today to investigate this opportunity to practice challenging medicine in a hospital-supported surrounding, while enjoying an incomparable lifestyle in one of the Northwest's most scenic areas. Competitive first year guarantees offered to the selected candidate. Interview and relocation expenses absorbed by the client. For complete details, contact Jim Murphy, Spectrum Search, PO Box 27352, St. Louis, MO 63141; 1 (800) 237-6906; (314) 878-2280.

NORTHERN CALIFORNIA, EMERGENCY MEDICINE. Full-time positions available in the Emergency Department at the University of California, Davis, Medical Center. The University serves a large region of northern California and is a major trauma center. Emergency physicians teach and supervise medical students and housestaff (240 per year) in addition to treating patients. Emergency Department physicians also provide medical control for UCDMC Life Flight, director of base station activities, and are actively involved in trauma care. Opportunities exist for involvement in other UCD School of Medicine teaching activities. Applicants should send CV to Robert W. Derlet, MD, Chief, Division of Emergency Medicine, University of California, Davis, Medical Center, 2315 Stockton Blvd, Sacramento, CA 95817.

(Continued on Page 124)

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(Continued from Page 114)

February 11-13—**21st Annual Recent Advances in Neurology.** UCSF at Fairmont Hotel, San Francisco. Thurs-Sat. 15 hrs. Contact: UCSF.

February 12-13—**Comprehensive Care of the AIDS Patient: A Workshop.** UCSF. Fri-Sat. Contact: UCSF.

February 13-15—**New Precepts and Concepts in Dermatopathology.** Desert Hospital, Palm Springs. Sat-Mon. 14 hrs. $350. Contact: Charles Steffen, MD, 1111 Tahquitz East, Ste 102A, Palm Springs 92262. (619) 325-5588.

February 15-17—**Recent Advances in Geriatric Rehabilitation: What Is It? Who Needs It? What Works?** UCSD at Holiday Inn at the Embarcadero, San Diego. Mon-Wed. 18 hrs. $295. Contact: UCSD.

February 15-17—**8th Annual Betty Ford Center Conference on Alcoholism/Chemical Dependency: Integrating Concerns in Chemical Dependency.** Annenberg Center for Health Sciences and the Betty Ford Center. Mon-Wed. 13.5 hrs. Contact: Annenberg Center, 39000 Bob Hope Drive, Rancho Mirage 92270-3298. (800) 321-3690-national; (800) 621-7322-Calif.

February 15-17—**Clinical Hematology and Oncology: 1988.** Scripps Clinic and Research Foundation at San Diego Princess Resort. Mon-Wed. Contact: Bonny Mower, 10666 N. Torrey Pines Road, La Jolla, 92037. (619) 457-8556.

February 18-19—**Video Display Terminal Safety.** USC. Thur-Fri. $265. Contact: USC.

February 19-21—**Diagnosis and Management of Respiratory Disease.** Medical Education Resources at Wyndham Hotel, Palm Springs. Fri-Sat. 11-13 hrs. $225-$295. Contact: MER, 5808 S. Rapp St., Suite 202, Littleton, CO 80120. (800) 421-3756.

February 19-21—**New Precepts and Concepts in Dermatopathology.** Desert Hospital, Palm Springs at Desert Hospital. Fri-Sun. 14 hrs. $350. Contact: Charles Steffen, MD, 1111 Tahquitz East, Ste 102A, Palm Springs 92262.

March 2-5—**Annual Review in Family Medicine: Controversies and Challenges in Primary Care.** UCSF at Stanford Court Hotel, San Francisco. Wed-Sat. 17 hrs. Contact: UCSF.

March 4—**6th Annual Geriatrics Symposium.** Sutter Health at Red Lion Inn, Sacramento. Fri. 7 hrs. Contact: Sutter Health, CME Dept. 2020 I St, Suite D, Sacramento 95814. (916) 446-7681.

March 4—**14th Annual Diabetes Program.** UCD at Capitol Plaza Holiday Inn, Sacramento. Contact: UCD.

March 4-9—**Western Scientific Assembly.** CMA at Bally's Hotel, Reno, Nevada. Thur-Sun. Contact: Susan Schaefer, CMA, P.O. Box 7690, San Francisco, 94120-7690. (415) 863-5522 Ext. 404.

March 4-10—**56th Annual Postgraduate Convention.** LLU. Fri-Thur. 35 hrs. Contact: LLU.

March 9—**Environmental and Occupational Medicine Symposium.** Enloe Memorial Hospital and Chico Community Hospital at The Esplanade Building, Enloe Hospital, Chico. Wed. 6 hrs. Contact: Bonnie Wells, 5th Ave and the Esplanade, Chico 95926. (916) 891-7375.

March 11-12—**Sleep Disorders Medicine: Medical Management.** Scripps Clinic and Research Foundation. Fri-Sat. 12 hrs. $200. Contact: Bonny Mower, 10666 N. Torrey Pines Road, La Jolla, 92037. (619) 457-8556.

March 11-12—**Diabetes Update.** UCSF at Holiday Inn Union Square, San Francisco. Fri-Sat. Contact: UCSF.

March 16-19—**5th Annual Horizon in Reproductive Health Medical Conference.** UCSD at Hotel Del Coronado, Coronado. Wed-Sat. Contact: Mary Fessel, 2100 5th Ave., San Diego, 90101. (619) 231-6760.

March 18-19—**Hematology: Neonatal, Pediatric and AIDS Related Issues.** Children's Hospital, Oakland at Berkeley Marina Marriott Hotel. Fri-Sat. 11 hrs. Contact: Kim Leadon, CME Department, Children's Hospital, 747 52nd St, Oakland 94609. (415) 428-3021.

March 19—**3rd Annual Symposium on Women's Health.** Sutter Health at Board of Realtors Building, Sacramento. Sat. 6 hrs. $45. Contact: Sutter Health, CME Department, 2020 I St, Suite D, Sacramento 95414. (916) 446-7681.

March 19—**Impatient Vs. Outpatient Treatment: How to Decide.** California Society for the Treatment of Alcoholism & Other Drug Dependencies at Ramada Renaissance Hotel, San Francisco. Sat. Contact: Corinne Parker, 3803 Broadway, Suite 2, Oakland, 94611. (415) 428-9091.

March 19-21—**Transfusion—Associated Infections and Immune Response.** UCSF at Fairmont Hotel, San Francisco. Sat-Mon. Contact: UCSF.

March 25—**Infectious Diseases for Pulmonary and Critical Care Specialists.** UCSF and Samuel Merritt Hospital at San Francisco. Fri. 7 hrs. $170. Contact: UCSF.

March 25-26—**Toxicology and Infectious Disease.** UCLA at San Diego Hilton Beach & Tennis Resort. Fri-Sat. 9 hrs. $146.25. Contact: UCLA.

March 26-April 2—**Orthopedic Emergencies.** Scripps Memorial Hospital, Encinitas and American Institute of Postgraduate Education at Waiohai and Poipu Beach Hotels, Kauai. One week. 21 hrs. $395. Contact: Edith S. Bookstein/AIPE, PO Box 2586, La Jolla 92038. (619) 454-3212.

March 26-April 2—**Behavioral Medicine for the Family Physician.** University of Arizona at Kona, Hawaii. One week. 24 hrs. Contact: Kathy Rairigh, Epic Expeditions, P.O. Box 209, Sun Valley, Idaho 83353. (208) 788-4995.

April 10-15—**Advanced Methods in Pharmacokinetics and Pharmacodynamics.** UCSF. Sun-Fri. Contact: UCSF.

April 13-15—**9th Annual Advances in Infectious Diseases: Current Therapy.** UCSF at Sheraton-Palace Hotel, San Francisco. Wed-Fri. 16 hrs. $365. Contact: UCSF.

April 13-17—**Annual Scientific Program and Postgraduate Courses.** Pacific Coast Fertility Society at Desert Princess Resort, Palm Springs. Wed-Sun. 22 hrs. Contact: Pacific Coast Fertility Society, 5820 Wilshire Blvd, #500, Los Angeles 90036. (213) 937-5514.

April 15-17—**Office Orthopedics for the Primary Care Physicians.** CMEA & Sharp Memorial Hospital at San Diego Princess Hotel. Fri-Sun. 20 hrs. $395. Contact: Jacqueline Shiller, P.O. Box 84296, San Diego, 92138. (619) 223-2997.

April 16-23—**Current Concepts in Allergy and Clinical Immunology.** University of Washington at Maui, Hawaii. One week. Contact: U/W School of Medicine, Div of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

April 23—**Current Concepts in Liver Diseases.** Scripps Clinic and Research Foundation at Amphitheater, Scripps Clinic, La Jolla. Thur. 6 hrs. $125. Contact: Bonny Mower, 10666 N. Torrey Pines Road, La Jolla, 92037. (619) 457-8556.

May 6-8—**Diagnosis and Management of Respiratory Diseases.** Medical Education Resources at Ceasars Palace, Las Vegas, Nevada. Fri-Sun. 11-13 hrs. $225-$295. Contact: MER, 5080 S. Rapp St., Suite 202, Littleton, CO 80120. (800) 421-3756.

May 15-20—**Primary Care Medicine: Update '88.** UCSF at the Waiohai Hotel, Hawaii. Sun-Fri. 20 hrs. $425. Contact: UCSF.

May 26-27—**Current Concepts of Anatomic Pathology.** UCSF. Thur-Fri. Contact: UCSF.

June 13-17—**Family Practice Refresher Course.** UCI at Sheraton Newport, Newport Beach. Mon-Fri. 44.5 hrs. $575. Contact: UCI.

June 13-18—**UCI Family Practice Refresher Course.** UCI and Memorial Medical Center at Sheraton Newport Hotel, Newport Beach. Mon-Sat. Contact: Memorial Medical Center, PO Box 1428, Long Beach 90801-1428. (213) 595-3811.

June 18-19—**Skills Workshop: Flexible Sigmoidoscopy and Colposcopy.** UCI at Sheraton Newport, Newport Beach. Sat-Sun. 16 hrs. $140-ea., $250-both. Contact: UCI.

June 25-26—**10th Annual Poison Control Center Symposium on Toxicology and Poisoning.** UCSF and Continuing Medical Education in Pharmacy at San Francisco. Sat-Sun. 14 hrs. $235. Contact: Continuing Education S/P, UCSF, Box 0446, San Francisco 94143. (415) 476-4194.

July 15-18—**Caring for People with AIDS and Their Loved Ones.** Concern for Dying: an Educational Council, at Bishop's Ranch, Healdsburg. Fri-Mon. Contact: Penny Weingarten, 250 West 57th St., Room 831, New York, NY 10107. (800) 248-2122.

IDAHO

February 13-20—**Controversies in Pulmonary Medicine.** University of Arizona College of Medicine, Department of Family and Community Medicine, and Epic Expeditions at Sun Valley. One week. 24 hrs. Contact: Kathy Rairigh, PO Box 209, Sun Valley 83353. (208) 788-4995.

(Continued on Page 120)

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(Continued from Page 118)

February 20-27—**Drug Therapy in Maternal-Fetal Medicine.** University of Washington School of Medicine at Sun Valley. One week. Contact: U/W School of Medicine, Div of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

February 20-27—**Effective Treatment of Common Sports Injuries.** University of Arizona College of Medicine, Department of Family and Community Medicine, and Epic Expeditions at Sun Valley. One week. 24 hrs. Contact: Kathy Rairigh, PO Box 209, Sun Valley 83353. (208) 788-4995.

March 4-6—**29th Annual Medical Winter Clinics—"You and Your Health."** Ada County Medical Society at Shore Lodge—Brundage Mountain for Alpine Powder and Nordic Skiing, McCall, Idaho. Fri-Sun. 11 hrs. $125. Contact: Judy Barningham, Ada County Medical Society, PO Box 2668, Boise 83701. (208) 336-2930.

March 12-19—**Strategies for Fitness and Health Promotion.** University of Arizona College of Medicine, Department of Family and Community Medicine, and Epic Expeditions at Sun Valley. One week. 24 hrs. Contact: Kathy Rairigh, PO Box 209, Sun Valley 83353. (208) 788-4995.

March 17-18—**Idaho Thoracic Society—Annual Medical Symposium.** Anderson Center, Boise. Contact: Idaho Thoracic Society, 2621 Camas St, Boise 83705. (208) 344-6567.

MONTANA

February 18-20—**7th Annual Big Sky Pulmonary Ski Conference.** American Lung Association of Montana at Big Sky of Montana. Thurs-Sat. Contact: ALA of Montana, 825 Helena Ave, Helena 59601. (406) 442-6556 or 1 (800) 252-6368 (in Montana).

NEW MEXICO

Information, requests for accreditation and items to be listed should be sent to the chairman of the CME Committee, New Mexico Medical Society, 303 San Mateo NE, Suite 204, Albuquerque, NM 87108 at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 266-7868.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

January 15-17—**Essentials of Health Care for Elderly: Clinical Evaluation and Management** (Session II). UNM Conference Center, Albuquerque. Contact: UNM SOM, Office of CME, (505) 277-3942.

January 23-24—**6th Annual Winter Family Practice Meeting.** Marriott Hotel, Albuquerque. Contact: New Mexico Chapter, American Academy of Family Physicians, PO Box 23070, Albuquerque 87192. (505) 298-5300.

January 28-29—**Humane Care and Use of Laboratory Animals.** Sheraton Old Town, Albuquerque. Contact: UNM SOM, Office of CME, (505) 277-3942.

February 12-14—**Case Studies in Cardiology.** Presbyterian Heart Institute, Albuquerque. Contact: (505) 841-1065/(505) 242-2796.

February 25-27—**21st Annual OB/GYN Postgraduate Seminar.** Holiday Inn Pyramid Plaza, Albuquerque. Contact: UNM SOM, Office of CME, (505) 277-3942.

February 25-27—**Santa Fe Ski Symposium—Hypertension—1988.** Santa Fe. Thurs-Sat. Contact: National Kidney Foundation of New Mexico, 1715 Girard, NE, Albuquerque 87106. (505) 266-4573.

February 26-28—**16th Annual Thoracic Society Lung Disease Symposium.** Santa Fe Hilton. Fri-Sun. Contact: Lung Association, (505) 265-0732.

March 2-5—**Taos Metabolism Seminar.** Quail Ridge Inn, Taos. Contact: Martin J. Conway, MD, Lovelace Medical Center, 5400 Gibson SE, Albuquerque 87108. (505) 262-7000.

March 4-5—**Advances in Internal Medicine '88.** Veterans Administration Medical Center, Albuquerque. Contact: UNM SOM, Office of CME, (505) 277-3942.

March 11—**The Physician in Crisis.** Presbyterian Hospital Quality of Life Committee. Contact: Office of Medical Education, (505) 841-1225.

March 12—**NM Pediatric Society Wylder Lecture—Mother to Child Infection.** UNM School of Pharmacy Auditorium. Contact: Marilyn Stark, NM Pediatric Society, (505) 265-7431.

April 21-23—**10th Annual Pediatric Cardio-Pulmonary Update.** Sheraton Old Town, Albuquerque. Contact: UNM SOM, Office of CME, (505) 277-3942.

April 29-May 1—**Southwest Allergy Forum.** Eldorado Hotel, Sante Fe. Contact: UNM SOM, Office of CME, (505) 277-3942.

May 5-7—**NM Medical Society Annual Meeting—AIDS—Protecting the Health Professional** and **Chemical Dependency, Monitored Treatment Program. Loss Control Seminar,** Physicians Mutual Liability Insurance Co. Albuquerque Hilton Inn. Contact: NM Medical Society, (505) 266-7868.

May 14—**Cardiac Physical Diagnosis Symposium.** Contact: UNM SOM, Office of CME, (505) 277-3942.

May 19-20—**Mental Health Services With Hispanic and Native American Children and Families.** Contact: UNM SOM, Office of CME, (505) 277-3942.

June 2-3—**8th Annual UNM/ACEP Emergency Medicine Symposium.** AMFAC Hotel, Albuquerque. Contact: UNM SOM, Office of CME, (505) 277-3942.

July 22-24—**Diagnosis and Management of Arrhythmia.** Contact: Presbyterian Heart Institute, Albuquerque, (505) 841-1065/(505) 242-2796.

UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the CME office of the Utah Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. They also must meet the definition of Utah Approved CME Credit for the purpose of medical license reregistration in Utah. Accredited institutions wishing to list AMA Category 1/Utah Approved CME courses here should send information at least two months in advance to the Office of Continuing Medical Education, 540 East Fifth South, Salt Lake City, Utah 84102; or phone (801) 355-5290. For information on CME accreditation or on the CME requirements of the Utah Physicians' Licensing Board, please write the CME office at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution or the CME office for current details.

MEDICAL GRAND ROUNDS

Each Wed—8:00-9:00 a.m. Alternating between University of Utah Medical Center and VA Medical Center, Salt Lake City. Contact: William D. Odell, MD, PhD, Professor and Chairman, Dept of Internal Medicine, Univ of Utah, (801) 581-7606.

* * *

January 15-16—**Psychiatric Gerontology: Depression in the Elderly** (Sponsor: UUMC). Fri-Sat. University Park Hotel, Salt Lake City. 12 hrs. Contact: Rosalie Lammle, (801) 581-8664.

January 16-18—**Arthroscopic Surgery 1988** (Sponsor: UUMC). Sat-Mon. Snowbird Resort. Contact: Robert Metcalf, MD, (801) 581-7601.

January 19-21—**Pulmonary Function Testing** (Sponsor: UUMC). Tues-Thurs. Contact: Connie Crandall, (801) 581-5710.

(Continued on Page 122)

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CONTINUING MEDICAL EDUCATION

(Continued from Page 120)

January 29-31—**Contemporary Approaches to Sexual Function/Dysfunction** (Sponsor: UUMC). Fri-Sun. Snowbird Resort. Contact: Claire Turner, (801) 581-5809.

January 31-February 3—**Pediatric Cardiology** (Sponsor: UUMC). Sun-Wed. Snowbird Resort. Contact: George Veasy, MD, (801) 521-1221.

February 7-12—**Vascular Imaging: Update on Interventional Radiology** (Sponsor: UUMC). Sun-Fri. Snowbird Resort. Contact: (801) 581-8188.

February 8-12—**4th Annual Surgical Pathology Ski Retreat** (Sponsor: UUMC). Mon-Fri. Park City Resort. Contact: Karen Rasmussen, (801) 268-7097.

February 8-13—**Family Practice Refresher Course** (Sponsor: UUMC). Mon-Sat. Salt Lake Sheraton. Contact: Kathy Chisholm, (801) 581-8634.

February 8-13—**Utah Ophthalmological Society Annual Winter Meeting** (Sponsor: UOS). Mon-Sat. Little America Hotel, Salt Lake City. 15 hrs. Contact: Carol Leavitt, (801) 355-7477.

February 15-19—**11th Annual Update in Clinical Microbiology and Immunology** (Sponsor: UUMC). Mon-Fri. Park City Resort. Contact: M. Beckman, (801) 581-7480.

February 17-20—**29th Annual OB-GYN Update** (Sponsor: UUMC). Wed-Sat. Snowbird Resort. Contact: Sheryl Martin, (801) 581-5501.

February 19-23—**33rd Annual Postgrad Course in Anesthesiology** (Sponsor: UUMC). Fri-Tues. Salt Lake City. Contact: Vicky Larsen, (801) 581-6393.

February 21-28—**Intermountain Dermatology Meeting** (Sponsor: UUMC). Sun-Sun. Colorado. Contact: Bernie Lasalle, (801) 581-7837.

February 24-27—**Reproductive Endocrinology and Infertility** (Sponsor: UUMC). Wed-Sat. Snowbird Resort. Contact: Sheryl Martin, (801) 581-5501.

February 24-27—**Pediatric Emergency Medicine** (Sponsor: UUMC). Wed-Sat. Salt Lake City. Contact: Amy Eschelman, (801) 521-1221.

SPONSORS OF COURSES—ABBREVIATIONS

AHA: American Heart Association, Utah Affiliate, 645 E 400 South, Salt Lake City 84102. (801) 322-5601.

BYUHS: Brigham Young University Health Services, McDonald Student Health Center, Brigham Young University, Provo 84602. (801) 378-2771.

CH: Castleview Hospital (formerly Carbon Hospital), RFD 2, Box 46, Price 84501. (801) 637-4800.

CWH: Cottonwood Hospital, 5770 S 300 East, Salt Lake City 84101. (801) 262-3461.

DMC: Dixie Medical Center, 544 S 400 East, St George 84770. (801) 673-9681.

HCH: Holy Cross Hospital, 1045 E First South, Salt Lake City 84102. (801) 350-4744.

ITS: Intermountain Thoracic Society, 1616 S 11th East, Salt Lake City 84105. (801) 484-4456.

LDSH: LDS Hospital, 8th Ave and "C" St, Salt Lake City 84143. (801) 321-1100.

LRH: Logan Regional Hospital, 1400 N 5th East, Logan 84321. (801) 752-2050.

MDH: McKay-Dee Hospital Center, 3939 Harrison Blvd, Ogden 84409. (801) 399-4141.

MVH: Mountain View Hospital, 1000 E Highway 6, Payson 84651. (801) 465-9201.

144: 144th Evacuation Hospital, PO Box 8000, Salt Lake City 84108. (801) 524-3924.

OSS: Ogden Surgical Society, PO Box 9311, Ogden 84409.

PCMC: Primary Children's Medical Center, 320 12th Ave, Salt Lake City 84103. (801) 363-1221.

PVH: Pioneer Valley Hospital, 3460 S 4155 West, West Valley City 84120. (801) 968-9061.

SMH: St Mark's Hospital, 1200 E 3900 South, Salt Lake City 84117. (801) 268-7111.

UOS: Utah Ophthalmological Society, 540 E 500 South, Salt Lake City 84102. (801) 355-7477.

USH: Utah State Hospital, PO Box 270, Provo 84603-0270. (801) 373-4400.

UUMC: University of Utah Medical Center, 50 N Medical Dr, Salt Lake City 84132. (801) 581-2258.

UVRMC: Utah Valley Regional Medical Center, 1034 N Fifth West, Provo 84604. (801) 373-7850.

VAMC: Veterans Administration Medical Center, 500 Foothill Dr, Salt Lake City 84148. (801) 582-1565.

VVMC: Valley View Medical Center, 595 S 75 East, Cedar City 84720. (801) 586-6587.

February 28-March 4—**Vascular Imaging: Update on Interventional Radiology** (Sponsor: UUMC). Sun-Fri. Snowbird Resort. Contact: (801) 581-8188.

February 29-March 4—**Advances in Internal Medicine** (Sponsor: UUMC). Mon-Fri. Snowbird Resort. Contact: Jennifer Fossum, (801) 581-3581.

March 7-11—**Gastroenterology Update** (Sponsor: UUMC). Mon-Fri. Snowbird Resort. Contact: Jennifer Fossum, (801) 581-3581.

March 1988—**Nutrition in Contemporary Medicine** (Sponsor: UUMC). Contact: Jennifer Fossum, (801) 581-3581.

March 30-April 1—**Common Problems in Pediatrics** (Sponsor: UUMC). Wed-Fri. Contact: K. Blosch, (801) 466-3500.

WASHINGTON

This listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. To list Category 1 programs here please send information at least two months in advance to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 900, Seattle, WA 98121; or phone (206) 441-WSMA.

Brochures and registration forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

January 20—**Health Effects of Wood Smoke.** Seattle. Wed. Contact: U/W, (206) 543-1069.

January 21—**Conjoined Conference: The Significance of Hematuria.** Spokane. Thurs. Contact: Jo Ann Lambert, (509) 458-7159.

January 22—**Biliary Tract Diseases—Stones and Tumors.** Seattle. Fri. Contact: VMMC.

January 28—**Conjoined Conference: Diagnosis and Management of Carcinoma of the Breast.** Spokane. Thurs. Contact: Jo Ann Lambert, (509) 458-7159.

January 29—**Silent Ischemia—Present Status.** Seattle. Fri. Contact U/W, (206) 543-1050.

January 29-30—**Orhital Problems and Treatment: Plastic and Reconstructive Surgery (WSAO Annual Meeting).** Seattle. Fri-Sat. Contact: Patti Smith, (206) 441-9762.

February 3-5—**Aging and the Elderly.** Seattle. Wed-Fri. Contact: Maria Lilja, (206) 543-1050.

February 5—**Esophageal Disorders in Clinical Practice.** Seattle. Fri. Contact: VMMC.

February 10-13—**Washington State Academy of Physician Assistants CME Conference.** Bellevue. Wed-Sat. Contact: Kory Diemert, (206) 441-9762.

February 19-20—**Medicine for Psychotherapists.** Seattle. Fri-Sat. Contact: VMMC.

February 25-26—**Survivorship.** Spokane. Thurs-Fri. Contact: Carolyn Hunter, (509) 325-6146.

COURSE SPONSORS AND CONTACT INFORMATION

CME HARBORVIEW—Contact: Gayle Splater, Cytology Continuing Education, Dept. of Pathology, Harborview Medical Center, 325 Ninth Avenue, Seattle, WA 98104. (206) 223-5953.

CME PIERCE COUNTY—Contact: Mrs Maxine Bailey, Executive Director, College of Medical Education, 705 South Ninth, No. 203, Tacoma, WA 98405. (206) 627-7137.

U/W (UNIVERSITY OF WASHINGTON)—Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

WSMA—Washington State Medical Association, Continuing Medical Education, 2033 Sixth Ave, Suite 900, Seattle, WA 98121. (206) 441-9762.

VMMC (VIRGINIA MASON MEDICAL CENTER)—Contact: Linda Orgel, Division of Continuing Medical Education, Virginia Mason Medical Center, PO Box 900, Seattle, WA 98111. (206) 223-6898.

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March 3-4—**Northwest Regional Rural Health Conference. Rural Health: Strategies and Solutions.** Spokane. Thurs-Fri. Contact: William Lassey, (509) 747-1012.

March 4-5—**Spokane Society of Internal Medicine—Annual CME Meeting: Weekend Athlete—Impact on Medical Practice in the 80s.** Spokane. Wed-Thurs. Contact: Curtis Wickre, MD, (509) 838-2531.

March 4-5—**Primary Care of Orthopaedics.** Seattle. Fri-Sat. Contact: Maria Lilja, (206) 543-1050.

March 4-5—**Soft Tissue Surgery.** Seattle. Fri-Sat. Contact: VMMC.

March 11—**Recent Developments in Occupational Medicine.** Fri. Contact: U/W, (206) 543-1069.

March 15—**Washington State Academy of Ophthalmology Monthly Meeting.** TBA. Tues. Contact: Patti Smith, (206) 441-9762.

March 18-19—**NW Regional Rural Health Conference. Rural Health: Strategies and Solutions.** Spokane. Fri-Sat. Contact: ICNE, (509) 325-6146.

March 19-23—**11th Annual Physical Medicine and Rehabilitation Review.** Seattle. Sat-Wed. Contact: Maria Lilja, (206) 543-1050.

March 19-23—**Death Investigation.** Seattle. Sat-Wed. Contact: Maria Lilja, (206) 543-1050.

March 19-26—**Advances in Drug Therapy.** Seattle. One week. Contact: U/W, (206) 543-1050.

March 23-25—**Spirometry Training for Worker Screening.** Seattle. Wed-Fri. Contact: U/W, (206) 543-1069.

March 24-25—**Current Issues in Nutrition.** Seattle. Thurs-Fri. Contact: U/W, (206) 543-1050.

March 25—**Update in Contrast Media: An Evening of Uroradiology.** Seattle. Fri. Contact: VMMC.

April 19—**Washington State Academy of Ophthalmology Monthly Meeting.** TBA. Tues. Contact: Pattie Smith, (206) 441-9762.

May 5-6—**Health Effects of Synthetic Fibers.** Seattle. Thurs-Fri. Contact: U/W, (206) 543-1069.

May 13—**Current Drug Topics—Pharmacology for the Practitioner.** Seattle. Fri. Contact: VMMC.

May 19-20—**Travel and Medicine.** Seattle. Thurs-Fri. Contact: Maria Lilja, (206) 543-1050.

May 19-21—**Emergency Medicine Update.** Seattle. Thurs-Sat. Contact: VMMC.

June 3—**Topics in General Internal Medicine.** Seattle. Fri. Contact: VMMC.

June 9-11—**Ohstetric Ultrasound.** Seattle. Thurs-Sat. Contact: Robin Murray, (202) 863-2543.

June 20-24—**Pathology of Lung Cancer.** Seattle. Mon-Fri. Contact: VMMC.

WYOMING

January 29-30—**Wyoming Medical Society—Annual Winter Seminar.** Holiday Inn, Cheyenne. 8 hrs. $100, members; $150, nonmembers. Contact: WMS, PO Box 4009, Cheyenne 82003-4009. (307) 635-2424.

February 28-March 6—**Strategies for Fitness and Health Promotion.** University of Arizona College of Medicine, Department of Family and Community Medicine, and Epic Expeditions at Jackson Hole. One week. 24 hrs. Contact: Kathy Rairigh, PO Box 209, Sun Valley, ID 83353. (208) 788-4995. ◆

A WORD TO THE WHYS

WHY AMA? The AMA can help you build and improve the efficiency of your practice through Practice Management seminars and audio visual courses. These programs are designed to assist you in every phase of your practice by providing you with practical information about business procedures and management techniques. Practice Management: it's one more good reason why you should be part of the AMA.

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To Join, Contact your county or state medical society or write: Division of Membership, AMA, 535 North Dearborn Street, Chicago, Illinois 60610 or call collect, (312) 751-6196.

(Continued from Page 116)

PHYSICIANS WANTED

Primary Care Physicians

Health Maintenance Organizations . . . they're what the future of health care is all about. And Maxicare is the largest investor-owned HMO. Our 2.3 million members are served by 60 health plans in 28 states.

Opportunities are currently available for Board Certified or Board Eligible Family Practioners, Pediatricians, and Internists to serve our members in the San Francisco East Bay Area.

Maxicare/HealthAmerica offers a competitive salary and benefits package including employee vacation, CME time and 401k plan. For immediate and confidential consideration, please send your C.V. to: Maxicare/HealthAmerica Northern California, Attn: Henry Loubet, Executive Director, Dept. WJM, 1 Bay Plaza, Suite 210, Burlingame, CA 94010. Equal Opportunity Employer.

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GENERAL SURGEON—BE/BC. Outstanding opportunity for aggressive surgeon with a highly profitable, well-established, fee-for-service, multispecialty clinic. 14 physicians on staff. Ready made practice. Unmatchable guaranteed salary first year, then ownership. New hospital. Wonderful family town with nationally recognized school system and unequalled outdoor recreation possibilities. Telephone calls will not be accepted. Send CV to John Brust, Mesaba Clinic, 1814 14th Ave East, Hibbing, MN 55746.

CHAIRMAN, DEPARTMENT OF INTERNAL MEDICINE, KERN MEDICAL CENTER. A county operated teaching hospital is seeking a chairman for this UCLA affiliated department. The department has nine full-time and part-time members, 18 residency positions all currently filled with quality graduates. Qualifications: BC in Internal Medicine, established record of scholarly achievement in teaching and patient care, demonstrated management skills to direct a fully accredited residency program in an active public hospital and relate to other programs at Kern Medical Center and the UCLA system. Candidate must be eligible for appointment to senior faculty position at UCLA and be licensed in the State of California. (The County of Kern is an Equal Opportunity Employer.) Address inquiries with CV to Paul Toot, MD, Chairman, Internal Medicine Search Committee, Kern Medical Center, 1830 Flower St, Bakersfield, CA 93305.

NEW MEXICO—FAMILY PHYSICIAN. Innovative practice in New Mexico mountain community needs third BC/BE FP. Salary guarantee with reasonable work schedule. Video available showing our practice style, area, and people. Gila Family Care, 1121 West St, Silver City, NM 88061.

PHYSICIANS WANTED

INTERNIST, BC, to join four others in a busy practice in pleasant Sierra foothills community. Abundant recreational opportunities, yet near urban centers. Contact Dennis Nousaine, MD, FACP, 815 Court St, Ste 7, Jackson, CA 95642.

FAMILY PRACTITIONER. Visalia Medical Clinic has an opening for a BC/BE Family Practitioner to join a four physician department. Located in the San Joaquin Valley of California, serving a market area of approximately 350,000 citizens, the Visalia Medical Clinic is a 40 physician multispecialty clinic. Excellent hospital services and facilities. Compensation is incentive oriented with advancement to full partnership after one year. Excellent fringe benefits. John G. Heinsohn, Administrator, 5400 W. Hillsdale, Visalia, CA 93291; (209) 733-5222.

UTAH. Full-time physicians needed for urgent care centers in Ogden area. Send CV to Val Rollins, MD, Emergency Department, St. Benedicts Hospital, 5475 S. 500 East, Ogden, UT 84405; or call (801) 479-2376.

INTERNIST NEEDED FULL-TIME. Primary Care position for Board certified Internist is now available with a growing San Francisco Health Plan. The position includes both inpatient and outpatient responsibilities. Send CV to Medical Director, French Health Plan, 4131 Geary Blvd, San Francisco, CA 94118.

INTERNAL MEDICINE—CENTRAL UTAH. Seeking General Internist and/or Internist with subspecialty in Endocrinology or Infectious Disease to join established Internal Medicine clinic. 350-bed hospital across the street. First year salary with possible partnership after first year. Inquire: Dorothy Farnworth, Central Utah Medical Clinic, 1055 North 500 West, Provo, UT 84601.

THE IRVINE MEDICAL CENTER AND THE UNIVERSITY OF CALIFORNIA-IRVINE, DEPARTMENT OF RADIOLOGICAL SCIENCES are seeking a full-time faculty member for the Department of Radiological Sciences at the Clinical Associate Professor or Clinical Professor level who would be assigned as Director of the Department of Radiology at Irvine Medical Center. The Irvine Medical Center is a new 177-bed hospital currently under construction in Irvine, California. Hospital opening is scheduled for fall of 1988. Administrative experience and academic background, including teaching and/or research, is required. Please send CV and the names of five references to Richard M. Friedenberg, MD, Professor and Chairman, Department of Radiological Sciences, University of California, Irvine, 101 City Drive South, Orange, CA 92668. The University of California is an Affirmative Action and an Equal Opportunity Employer.

CALIFORNIA, SAN FRANCISCO BAY AREA. Full-time career Emergency Physician wanted for high volume Emergency department. Emergency Medicine BC/BE mandatory to participate in a group of twenty full-time staff physicians seeing over 300 patients per day. Salaried position, excellent benefits include three weeks paid vacation, one week CME, paid malpractice, health and life insurance, corporate shareholdership in three years. Send CV or contact David Gallagher, MD, 27400 Hesperian Blvd, Hayward, CA 94545.

TUOLUMNE. Sierra Foothills, Yosemite area—base station hospital with 12,000 visits per year. Openings for experienced Emergency Room MDs. Outstanding mountain, recreation area in the heart of California gold country. Fee-for-service approximately $40 per hour or greater. Please send CV to Art B. Wong, MD, FACEP, Emergency Physicians' Medical Group, 1 Maritime Plaza, Ste 710, San Francisco, CA 94111.

CARDIOLOGIST, BC/BE. Invasive Cardiologist with PTCA skills to join two FACC Cardiologists in expanding ten physician Internal Medicine group in San Diego. Position available July 1988 or sooner. Reply with CV, statement of interest, and three letters of reference, to F. C. Millward, Administrator, 5111 Garfield St, La Mesa, CA 92041.

PHYSICIANS WANTED

SOUTHERN CALIFORNIA

Enjoy professional challenge and growth with a successful and expanding HMO in southern California. CIGNA Healthplans of California is seeking Specialists and Primary Care physicians committed to concepts of prevention and health maintenance to join our facilities in Los Angeles and Orange Counties. We offer an excellent compensation and benefits package including profit sharing. For consideration, please forward CV to:

Director/Physician Recruitment
CIGNA Healthplans of California
505 N. Brand Blvd, Suite 400-49
Glendale, CA 91203

INTERNIST. To join two Primary Care Internists in private practice in beautiful far-northern California one hour below major center. Midway between Portland and San Francisco, we have a rural setting with sophisticated practice and excellent hospital facilities. Subspecialty interest desirable within primary care framework. Salary and benefits with partnership an early goal. CV and your interests to R. H. Alley, Jr, MD, 105 Oberlin Rd, Yreka, CA 96097.

CALIFORNIA. BE/BC Internist to join staff of eight Internists in 15 physician multispecialty group located in central San Joaquin Valley. Competitive starting salary and full benefits. Excellent living and practice environment. Send CV to David A. Hellstern, Administrator, Kaweah Medical Group, Inc., 222 W. Willow, Visalia, CA 93291.

BC/BE CARDIOLOGIST. To join three invasive/noninvasive Cardiologists in practice, Portland, Oregon metropolitan area. Send CV to Number 76, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

ONCOLOGIST/INTERNIST. BC/BE to join 21 physician primary care and multispecialty group practice in beautiful Pacific Northwest setting. Reply to Shane Spray, 1400 E. Kincaid, Mount Vernon, WA 98273; (206) 428-2524.

CALIFORNIA. BC/BE Pediatrician to join staff of three Pediatricians in 15 physician multispecialty group located in central San Joaquin Valley. Competitive starting salary and full benefits. Excellent living and practice environment. Send CV to David A. Hellstern, Administrator, Kaweah Medical Group, Inc., 222 W. Willow St, Visalia, CA 93291.

ESTABLISHED BC FAMILY PRACTITIONER in south central Washington seeks BE/BC associate with OB interest. Practice in rural, family-oriented community serving area of 45,000. Income guarantee and assistance with relocation. Ski at White Pass. Fishing and other water sports on nearby Rimrock Lake and Columbia River. Contact PROSEARCH, 305 NE 102nd Ave, Portland, OR 97220; (503) 256-2070, ext 202.

BE/BC FAMILY PRACTICE physician wanted to join young successful BC Family Practitioner to start new group in northeastern Colorado community. Includes OB. Service area of 25,000. Generous first year income guarantee and assistance with relocation. Only one and one-half hours from Denver. Contact PROSEARCH, 305 NE 102nd Ave, Portland, OR 97220; (503) 256-2070, ext 202.

PACIFIC NORTHWEST, NEAR EUGENE, OREGON. BE/BC Internist wanted to join Family Practice group. Share call with Internists. Minimum salary guarantee. Good schools/outdoor recreation; University of Oregon/cultural events within 30 minutes. Contact John Hoopes, Cottage Grove Hospital, 1340 Birch St, Cottage Grove, OR 97424; (503) 942-0511.

CALIFORNIA—NORTH SAN FRANCISCO BAY AREA. Excellent opportunity for BC/BE Family Practitioner to join growing department. Flexible starting date. Multispecialty clinic emphasizing personalized care. Full hospital privileges including ICU/CCU. No obstetrics. Very favorable call schedule. Prepaid HMO practice provides excellent salary, benefits. Forward CV to Steven Freedman, MD, Kaiser Permanente, 1550 Gateway Blvd, Fairfield, CA 94533; (707) 427-4260.

PHYSICIANS WANTED

NEAR STANFORD. Six Internists, all subspecialty trained and members of clinical faculty at Stanford, interested in an Associate with subspecialty interest and training. Should be well grounded in Internal Medicine. Send CV to Dr Bigler, El Camino Internal Medical Group, 125 South Dr, Mountain View, CA 94040.

IDAHO. Family Practitioner with interest in OB wanted to join three Family Practitioners serving scenic northern Idaho community. Hospital provides complete assistance—office, salary, full benefits. BE/BC and cesarean section experience required. Enjoy outdoor recreation, rural life-style. Contact Jean Erickson, PROSEARCH, 305 NE 102nd Ave, Portland, OR 97220-4199; (503) 256-2070.

SAN FRANCISCO BAY AREA multispecialty group seeks Internist, BC/BE, to join 26 congenial men and women delivering quality care in a combined fee-for-service, HMO/PPO setting. Bay Valley Medical Group, Attn: Don Lass, 27212 Calaroga Ave, Hayward, CA 94545; (415) 785-5000.

FAMILY PRACTICE. San Diego. Primary care FP/IM wanted for busy community health center. Spanish speaking preferred. Send résumé to LHFHC, 1809 National Ave, San Diego, CA 92113 or contact Bea Romo (619) 234-8171.

SOUTH CENTRAL WASHINGTON COMMUNITY seeks BE/BC Internist for solo practice. Share office space with two other physicians. First year income guarantee and other assistance. Great income potential for right candidate! Progressive 38-bed hospital has CT services. Excellent schools and recreation. Contact PROSEARCH, 305 NE 102nd Ave, Portland, OR 97220; (503) 256-4488.

CALIFORNIA CENTRAL VALLEY. Desire BC/BE Family Practitioner to join busy two man Family Practice. Easy drive to San Francisco or mountains. Growing area; city of 40,000; good schools. Guarantee plus benefits. Reply to Number 59, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

PULMONARY INTERNIST. Practice opportunity in beautiful pacific northwest coastal town. BE/BC. Critical care skills needed. Must be affable and assertive. Send CV to Number 78, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

FAMILY PRACTITIONER—BC/BE. For Family Practice in a large central California community and migrant health center located in the San Joaquin Valley serving large Hispanic and Southeast Asian medically underserved population. Competitive salary with excellent fringe benefits and paid malpractice. Send CV and inquiries to Director, Sequoia Community Health Foundation, Inc., 2790 S. Elm Ave, Fresno, CA 93706.

EXCELLENT TEXAS OPPORTUNITIES in Cardiology, ENT, Family Practice (five), General Surgery, Internal Medicine (two), OB/GYN (four), Oncology, Orthopedic Surgery (three), Pediatrics (two), Vascular Surgery, Industrial Medicine. Excellent quality of life, first year guarantee, etc. Reply with CV or call Armando L. Frezza, Medical Support Services, 8806 Balcones Club Dr, Austin, TX 78750; (512) 331-4164.

NORTHERN CALIFORNIA OB/GYN. Beautiful Marin County, California OB/GYN practice looking for BC/BE female/male OB/GYN who is interested in joining a busy and successful practice of two MDs, one midwife, and four NPs. Progressive, busy OB practice offering family centered maternity care. Pro-choice philosophy. Opportunity for university affiliation. Lovely physical facilities with potential for investment. Must be well trained, enjoy working hard, committed to women's health care and fun to work with. Compensation package with partnership available in one year. Six weeks time off each year. Send résumé to WHMA/NEB, PO Box 1773, Ross, CA 94957.

PHYSICIANS WANTED

PHYSICIANS
Ambulatory Care Clinics

John Short & Associates, Inc., an internationally recognized health care management and consulting firm, is actively seeking **PHYSICIANS** with experience and credentials in **FAMILY MEDICINE/GENERAL PRACTICE** and **PRIMARY CARE SPECIALTIES.**

Full or part-time positions are available in San Diego to staff an existing Primary Care Clinic. In addition, JSA is accepting CV's in preparation for potential sites throughout the state of California. Qualifications, except for General Practitioners, include Board Certification or Board Eligibility.

John Short & Associates Inc. offers competitive compensation including paid malpractice insurance, professional development fund and incentive programs. **For additional information please contact: Susan Bray, Recruiting Director, John Short & Associates, Inc., Box 1305, Columbia, MD 21044.**

BC/BE INTERNIST to associate with General Surgeon, OB/GYN, Pediatrician, Internist, and three FPs in well-established rural practice. Send CV to R. F. LeBlond, MD, Park Clinic, Box 1139, Livingston, MT 59047.

INTERNIST. Live in San Francisco and commute to nearby rural area for four two-night shifts per month in combined Internal Medicine/Emergency room practice. Four Internists currently working in stable group. Practice quality medicine in the country where you can make a greater impact and enjoy lots of free time wherever you like to live. 72k per year. Charles Rath, MD, 199 E. Webster St, Colusa, CA 95932; (916) 458-7739.

NORTHERN SAN FRANCISCO BAY AREA: Seeking Physician BC/BE in Internal Medicine for Internist position in growing department. Kaiser Permanente Medical Center, 1550 Gateway Blvd, Fairfield, CA 94533; (707) 427-4200.

WALK-IN PHYSICIAN WANTED. ER/Primary Care training preferred, outstanding opportunity to start new department in rapidly growing multispecialty fee-for-service clinic in east San Gabriel Valley. Excellent salary and incentives. Send CV or call Mr Ghormley, Administrator, 420 W. Rowland St, Covina, CA 91723; (818) 331-6411.

RADIOLOGIST. To share small outpatient practice with one Radiologist in Grass Valley, California in the Sierra Nevada foothills. Experience in ultrasound and mammography necessary. No CT or nuclear medicine. Reply to Jack M. Scott, MD, 150 Catherine Lane, Grass Valley, CA 95945; (916) 272-3421.

MOUNTAIN LIVING! Family Practice Physician needed for dynamic group practice in Cuba, New Mexico. BC/BE with OB desired. Competitive salary and benefit package offered. Malpractice provided. Our unique climate allows you to ski in the morning and golf in the afternoon! Write or call: Mary Consie, Recruiter, New Mexico Health Resources, PO Box 27650, Albuquerque, NM 87125; (505) 242-0633.

PHYSICIANS WANTED

EMERGENCY GROUP seeking career oriented ACLS, ATLS physician for immediate opening. Moderate volume, income $120,000. Great outdoor activities including fishing, boating, skiing and sailing in south central Washington. Send CV to KEP, PO Box 6192, Kennewick, WA 99336; or call (509) 627-1798.

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Arizona Medical Association, Inc—810 W Bethany Home Rd, Phoenix 85013. (602) 246-8901. Annual Meeting: June 9-11, 1988, Loew's Ventana Canyon Resort, Tucson.

California Medical Association—PO Box 7690, San Francisco 94120-7690. (415) 863-5522. Annual Meeting: March 4-9, 1988, Bally's Grand Hotel, Reno.

Colorado Medical Society—PO Box 17550, Denver 80217-0550. (303) 779-5455. Annual Meeting: 1988, date and place to be announced.

Hawaii Medical Association—320 Ward Ave, Suite 200, Honolulu 96814. (808) 536-7702. Annual Meeting: October 10-12, 1987, Kauai Surf, Kauai.

Idaho Medical Association—305 W Jefferson, PO Box 2668, Boise 83701. (208) 344-7888. Annual Meeting: 1988, date and place to be announced.

Montana Medical Association—2012 11th Ave, Suite 12, Helena 59601. (406) 443-4000. Annual Meeting: 1988, date and place to be announced.

Nevada State Medical Association—3660 Baker Lane, Reno 89502. (702) 825-6788. Annual Meeting: April 21-24, 1988, Laughlin.

New Mexico Medical Society—303 San Mateo NE, Suite 204, Albuquerque 87108. (505) 266-7868. Annual Meeting: May 5-7, 1988, Hilton Inn, Albuquerque.

Oregon Medical Association—5210 SW Corbett Ave, Portland 97201. (503) 226-1555. Annual Meeting: (House of Delegates only): November 6-8, 1987, Portland.

Utah Medical Association—540 E Fifth South, Salt Lake City 84102. (801) 355-7477. Annual Meeting: 1988, date and place to be announced.

Washington State Medical Association—900 United Airlines Bldg, 2033 6th Ave, Seattle 98121. (206) 441-WSMA. Annual Meeting: 1988, date and place to be announced.

Wyoming Medical Society—PO Drawer 4009, Cheyenne 82003-4009. (307) 635-2424. Annual Meeting: June 23-26, 1988, Jackson Lake Lodge, Moran.

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INDICATIONS AND USAGE: Rocephin is indicated for the treatment of the following infections when caused by susceptible organisms

LOWER RESPIRATORY TRACT INFECTIONS caused by *Strep pneumoniae, Streptococcus* species (excluding enterococci), *Staph aureus, H influenzae, H parainfluenzae, Klebsiella* species (including *K pneumoniae*), *E coli, E aerogenes, Proteus mirabilis* and *Serratia marcescens*

SKIN AND SKIN STRUCTURE INFECTIONS caused by *Staph aureus, Staph epidermidis, Streptococcus* species (excluding enterococci), *E cloacae, Klebsiella* species (including *K pneumoniae*), *Proteus mirabilis* and *Pseudomonas aeruginosa*

URINARY TRACT INFECTIONS (complicated and uncomplicated) caused by *E coli, Proteus mirabilis, Proteus vulgaris, M morganii* and *Klebsiella* species (including *K pneumoniae*)

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BACTERIAL SEPTICEMIA caused by *Staph aureus, Strep pneumoniae, E coli, H influenzae* and *K pneumoniae*

BONE AND JOINT INFECTIONS caused by *Staph aureus, Strep pneumoniae, Streptococcus* species (excluding enterococci), *E coli, P mirabilis, K pneumoniae* and *Enterobacter* species

INTRA-ABDOMINAL INFECTIONS caused by *E coli* and *K pneumoniae*

MENINGITIS caused by *H influenzae, N meningitidis* and *Strep pneumoniae* Ceftriaxone has also been used successfully in a limited number of cases of meningitis and shunt infections caused by *Staph epidermidis* and *E coli*

SURGICAL PROPHYLAXIS Preoperative administration of a single 1 gm dose may reduce incidence of postoperative infections in patients undergoing surgical procedures classified as contaminated or potentially contaminated (e g , vaginal or abdominal hysterectomy) and in those for whom infection at the operative site presents serious risk (e g , during coronary artery bypass surgery)

Although ceftriaxone has been shown to have been as effective as cefazolin in the prevention of infection following coronary artery bypass surgery no placebo-controlled trials have been conducted to evaluate any cephalosporin antibiotic in the prevention of infection following coronary artery bypass surgery When administered before indicated surgical procedures, a single 1 gm dose provides protection from most infections due to susceptible organisms for duration of procedure

SUSCEPTIBILITY TESTING Before instituting treatment with Rocephin, appropriate specimens should be obtained for isolation of the causative organism and for determination of its susceptibility to the drug Therapy may be instituted prior to obtaining results of susceptibility testing

CONTRAINDICATIONS: Rocephin is contraindicated in patients with known allergy to the cephalosporin class of antibiotics

WARNINGS: BEFORE THERAPY WITH ROCEPHIN IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE TO DETERMINE WHETHER THE PATIENT HAS HAD PREVIOUS HYPERSENSITIVITY REACTIONS TO CEPHALOSPORINS PENICILLINS OR OTHER DRUGS THIS PRODUCT SHOULD BE GIVEN CAUTIOUSLY TO PENICILLIN-SENSITIVE PATIENTS ANTIBIOTICS SHOULD BE ADMINISTERED WITH CAUTION TO ANY PATIENT WHO HAS DEMONSTRATED SOME FORM OF ALLERGY, PARTICULARLY TO DRUGS SERIOUS ACUTE HYPERSENSITIVITY REACTIONS MAY REQUIRE THE USE OF SUBCUTANEOUS EPINEPHRINE AND OTHER EMERGENCY MEASURES

Pseudomembranous colitis has been reported with the use of cephalosporins (and other broad-spectrum antibiotics), therefore, it is important to consider its diagnosis in patients who develop diarrhea in association with antibiotic use

Treatment with broad-spectrum antibiotics alters the normal flora of the colon and may permit overgrowth of clostridia Studies indicate a toxin produced by *Clostridium difficile* is one primary cause of antibiotic-associated colitis Cholestyramine and colestipol resins have been shown to bind to the toxin *in vitro*

Mild cases of colitis respond to drug discontinuance alone Moderate to severe cases should be managed with fluid, electrolyte and protein supplementation as indicated

When the colitis is not relieved by drug discontinuance or when it is severe, oral vancomycin is the treatment of choice for antibiotic-associated pseudomembranous colitis produced by *C difficile* Other causes of colitis should also be considered

Rarely, shadows suggesting sludge have been detected by sonograms of the gallbladder in asymptomatic and symptomatic patients This appears to be reversible on discontinuation of therapy In a few symptomatic patients receiving higher than usual doses, who underwent surgery, sludge containing traces of ceftriaxone was recovered from surgical specimens Discontinue therapy in patients who develop signs or symptoms suggestive of gallbladder disease, consider conservative management

PRECAUTIONS: *GENERAL*. Although transient elevations of BUN and serum creatinine have been observed, at the recommended dosages, the nephrotoxic potential of Rocephin is similar to that of other cephalosporins

Ceftriaxone is excreted via both biliary and renal excretion (see Clinical Pharmacology) Therefore, patients with renal failure normally require no adjustment in dosage when usual doses of Rocephin are administered, but concentrations of drug in the serum should be monitored periodically If evidence of accumulation exists dosage should be decreased accordingly

Dosage adjustments should not be necessary in patients with hepatic dysfunction, however, in patients with both hepatic dysfunction and significant renal disease, Rocephin dosage should not exceed 2 gm daily without close monitoring of serum concentrations

Alterations in prothrombin times have occurred rarely in patients treated with Rocephin Patients with impaired vitamin K synthesis or low vitamin K stores (e g , chronic hepatic disease and malnutrition) may require monitoring of prothrombin time during Rocephin treatment Vitamin K administration (10 mg weekly) may be necessary if the prothrombin time is prolonged before or during therapy

Prolonged use of Rocephin may result in overgrowth of nonsusceptible organisms Careful observation of the patient is essential If superinfection occurs during therapy, appropriate measures should be taken

Rocephin should be prescribed with caution in individuals with a history of gastrointestinal disease, especially colitis

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY Carcinogenesis Considering the maximum duration of treatment and the class of the compound, carcinogenicity studies with ceftriaxone in animals have not been performed The maximum

ROCEPHIN® (ceftriaxone sodium/Roche)

duration of animal toxicity studies was six months

Mutagenesis Genetic toxicology tests included the Ames test, a micronucleus test and a test for chromosomal aberrations in human lymphocytes cultured *in vitro* with ceftriaxone Ceftriaxone showed no potential for mutagenic activity in these studies

Impairment of Fertility Ceftriaxone produced no impairment of fertility when given intravenously to rats at daily doses up to 586 mg/kg/day approximately 20 times the recommended clinical dose of 2 gm/day

PREGNANCY Teratogenic Effects Pregnancy Category B Reproductive studies have been performed in mice and rats at doses up to 20 times the usual human dose and have no evidence of embryotoxicity fetotoxicity or teratogenicity In primates, no embryotoxicity or teratogenicity was demonstrated at a dose approximately three times the human dose

There are however no adequate and well-controlled studies in pregnant women Because animal reproductive studies are not always predictive of human response this drug should be used during pregnancy only if clearly needed

Nonteratogenic Effects In rats, in the Segment I (fertility and general reproduction) and Segment III (perinatal and postnatal) studies with intravenously administered ceftriaxone no adverse effects were noted on various reproductive parameters during gestation and lactation, including postnatal growth functional behavior and reproductive ability of the offspring at doses of 586 mg/kg/day or less

NURSING MOTHERS Low concentrations of ceftriaxone are excreted in human milk Caution should be exercised when Rocephin is administered to a nursing woman

PEDIATRIC USE Safety and effectiveness of Rocephin in neonates, infants and children have been established for the dosages described in the Dosage and Administration section *In vitro* studies have shown ceftriaxone like some other cephalosporins can displace bilirubin from serum albumin Exercise caution before administration to hyperbilirubinemic neonates, especially prematures

ADVERSE REACTIONS: Rocephin is generally well tolerated In clinical trials the following adverse reactions, which were considered to be related to Rocephin therapy or of uncertain etiology were observed

LOCAL REACTIONS pain, induration or tenderness at the site of injection (1%) Less frequently reported (less than 1%) was phlebitis after I V administration

HYPERSENSITIVITY—rash (1 7%) Less frequently reported (less than 1%) were pruritus, fever or chills

HEMATOLOGIC—eosinophilia (6%), thrombocytosis (5 1%) and leukopenia (2 1%) Less frequently reported (less than 1%) were anemia, neutropenia lymphopenia, thrombocytopenia and prolongation of the prothrombin time

GASTROINTESTINAL diarrhea (2 7%) Less frequently reported (less than 1%) were nausea or vomiting, and dysgeusia

HEPATIC—elevations of SGOT (3 1%) or SGPT (3 3%) Less frequently reported (less than 1%) were elevations of alkaline phosphatase and bilirubin

RENAL—elevations of the BUN (1 2%) Less frequently reported (less than 1%) were elevations of creatinine and the presence of casts in the urine

CENTRAL NERVOUS SYSTEM headache or dizziness were reported occasionally (less than 1%)

GENITOURINARY moniliasis or vaginitis were reported occasionally (less than 1%)

MISCELLANEOUS—diaphoresis and flushing were reported occasionally (less than 1%)

Other rarely observed adverse reactions (less than 01%) include leukocytosis, lymphocytosis, monocytosis, basophilia, a decrease in the prothrombin time, jaundice, gallbladder sludge, glycosuria, hematuria, anaphylaxis, bronchospasm, serum sickness, abdominal pain colitis, flatulence dyspepsia, palpitations and epistaxis

DOSAGE AND ADMINISTRATION: Rocephin may be administered intravenously or intramuscularly The usual adult daily dose is 1 to 2 gm given once a day (or in equally divided doses twice a day) depending on the type and severity of the infection The total daily dose should not exceed 4 grams

For the treatment of serious miscellaneous infections in children, other than meningitis, the recommended total daily dose is 50 to 75 mg/kg (not to exceed 2 grams), given in divided doses every 12 hours

Generally Rocephin therapy should be continued for at least two days after the signs and symptoms of infection have disappeared The usual duration is 4 to 14 days, in complicated infections longer therapy may be required

In the treatment of meningitis a daily dose of 100 mg/kg (not to exceed 4 grams), given in divided doses every 12 hours, should be administered with or without a loading dose of 75 mg/kg

For the treatment of uncomplicated gonococcal infections, a single intramuscular dose of 250 mg is recommended

For preoperative use (surgical prophylaxis), a single dose of 1 gm administered 1/2 to 2 hours before surgery is recommended

When treating infections caused by *Streptococcus pyogenes*, therapy should be continued for at least ten days

No dosage adjustment is necessary for patients with impairment of renal or hepatic function, however, blood levels should be monitored in patients with severe renal impairment (e g dialysis patients) and in patients with both renal and hepatic dysfunctions

HOW SUPPLIED: Rocephin (ceftriaxone sodium/Roche) is supplied as a sterile crystalline powder in glass vials and piggyback bottles The following packages are available

Vials containing 250 mg, 500 mg, 1 gm or 2 gm equivalent of ceftriaxone, piggyback bottles containing 1 gm or 2 gm equivalent of ceftriaxone, bulk pharmacy containers containing 10 gm equivalent of ceftriaxone (NOT FOR DIRECT ADMINISTRATION)

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NOTE Rocephin in the frozen state should not be stored above -20°C

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†Manufactured for Roche Laboratories, Division of Hoffmann-La Roche Inc , by Travenol Laboratories, Inc , Deerfield, Illinois 60015

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The portrait of anxiety

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WARNINGS
Not of value in psychotic patients. Caution patients against hazardous occupations requiring complete mental alertness and about the simultaneous ingestion of alcohol and other CNS depressant drugs.

Benzodiazepines can cause fetal harm in pregnant women. Warn patients of the potential hazard to the fetus. Avoid during the first trimester.

PRECAUTIONS
General: The dosage of XANAX Tablets should be reduced or withdrawn gradually, since withdrawal seizures have been reported upon abrupt withdrawal. If XANAX is combined with other psychotropics or anticonvulsant drugs, consider drug potentiation (see Drug Interaction section). Exercise the usual precautions regarding size of the prescription for depressed or suicidal patients. In elderly and debilitated patients, use the lowest possible dosage (see Dosage and Administration). Observe the usual precautions in treating patients with impaired renal or hepatic function.

Information for Patients: Alert patients about: (a) consumption of alcohol and drugs, (b) possible fetal abnormalities, (c) operating machinery or driving, (d) not increasing dose of the drug due to risk of dependence, (e) not stopping the drug abruptly. *Laboratory Tests*: Not ordinarily required in otherwise healthy patients. *Drug Interactions*: Additive CNS depressant effects with other psychotropics, anticonvulsants, antihistamines, ethanol and other CNS depressants. Pharmacokinetic interactions with other drugs, e.g., cimetidine, have been reported. *Drug/Laboratory Test Interactions*: No consistent pattern for a drug or test. *Carcinogenesis, Mutagenesis, Impairment of Fertility*: No carcinogenic potential or impairment of fertility in rats. *Pregnancy*: See Warnings. *Nonteratogenic Effects*: The child born of a mother on benzodiazepines may be at some risk for withdrawal symptoms and neonatal flaccidity. *Labor and Delivery*: No established use. *Nursing Mothers*: Benzodiazepines are excreted in human milk. Women on XANAX should not nurse. *Pediatric Use*: Safety and effectiveness in children below the age of 18 have not been established.

ADVERSE REACTIONS
Side effects are generally observed at the beginning of therapy and usually disappear with continued medication. In the usual patient, the most frequent side effects are likely to be an extension of the pharmacologic activity of XANAX, e.g., drowsiness or lightheadedness.

Central nervous system: Drowsiness, lightheadedness, depression, headache, confusion, insomnia, nervousness, syncope, dizziness, akathisia, and tiredness/sleepiness. *Gastrointestinal*: Dry mouth, constipation, diarrhea, nausea/vomiting, and increased salivation. *Cardiovascular*: Tachycardia/palpitations, and hypotension. *Sensory*: Blurred vision. *Musculoskeletal*: Rigidity and tremor. *Cutaneous*: Dermatitis/allergy. *Other side effects*: Nasal congestion, weight gain, and weight loss.

Withdrawal seizures have been reported upon rapid decrease or abrupt discontinuation of XANAX. (See Precautions.)

In addition, the following adverse events have been reported with the use of benzodiazepines: dystonia, irritability, concentration difficulties, anorexia, transient amnesia or memory impairment, loss of coordination, fatigue, sedation, slurred speech, jaundice, musculoskeletal weakness, pruritus, diplopia, dysarthria, changes in libido, menstrual irregularities, incontinence and urinary retention.

Paradoxical reactions such as stimulation, agitation, increased muscle spasticity, sleep disturbances, and hallucinations may occur. Should these occur, discontinue the drug.

During prolonged treatment, periodic blood counts, urinalysis, and blood chemistry analysis are advisable. Minor EEG changes, of unknown significance, have been observed.

DRUG ABUSE AND DEPENDENCE
Physical and Psychological Dependence: Withdrawal symptoms have occurred following abrupt discontinuance of benzodiazepines. Withdrawal seizures have occurred upon rapid decrease or abrupt discontinuation of therapy. In all patients, dosage should be gradually tapered under close supervision. Patients with a history of seizures or epilepsy should not be abruptly withdrawn from XANAX. Addiction-prone individuals should be under careful surveillance. *Controlled Substance Class*: XANAX is a controlled substance and has been assigned to schedule IV.

OVERDOSAGE
Manifestations include somnolence, confusion, impaired coordination, diminished reflexes and coma. No delayed reactions have been reported.

DOSAGE AND ADMINISTRATION
Dosage should be individualized.

The usual starting dose is 0.25 to 0.5 mg, t.i.d. Maximum total daily dose is 4 mg. In the elderly or debilitated, the usual starting dose is 0.25 mg, two or three times daily. Reduce dosage gradually when terminating therapy, by no more than 0.5 milligram every three days.

HOW SUPPLIED
XANAX Tablets are available as 0.25 mg, 0.5 mg, and 1 mg tablets.

Caution: Federal law prohibits dispensing without prescription. B-5-S

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- Discuss reimbursement/Medicare issues related to the pressure sore patient.
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***CAPOTEN® (captopril tablets) may be used as initial therapy only for patients with normal renal function in whom the risk of neutropenia/agranulocytosis is relatively low (1 out of over 8,600 in clinical trials). Use special precautions in patients with impaired renal function, collagen vascular disorders, or those exposed to other drugs known to affect the white cells or immune response. Evaluation of hypertensives should always include assessment of renal function. Overall, the most frequently occurring adverse reactions associated with CAPOTEN are skin rash and taste alteration; both effects are generally mild, reversible, or self-limited. See INDICATIONS AND USAGE, WARNINGS, and ADVERSE REACTIONS in the brief summary on the adjacent page.**

1. Croog SH, Levine S, Testa MA, et al: The effects of antihypertensive therapy on the quality of life. N Engl J Med 314(26):1657-1664, 1986.

SQUIBB

Means a job well done.

We spend so much of our lives at work...it's no wonder our work performance is key to our quality of life. Work performance is also a key factor in assessing antihypertensive therapy. CAPOTEN improved hypertensive patients' work performance (e.g., ability to keep pace with the job, concentration, job satisfaction, less on-the-job fatigue).[1] So, for hypertensive patients who work, why not prescribe the antihypertensive that can work for them... CAPOTEN.

These data are based on a multicenter, randomized, 24-week study of 626 mild-to-moderate hypertensive male patients with normal renal function, 181 of whom received captopril.

OF LIFE

THE CAPOTEN® (captopril tablets) DIFFERENCE

QUALITY OF LIFE THE CAPOTEN® (captopril tablets) DIFFERENCE

CAPOTEN® TABLETS

Captopril Tablets

INDICATIONS: Hypertension – CAPOTEN (captopril) is indicated for the treatment of hypertension. Consideration should be given to the risk of neutropenia/agranulocytosis (see WARNINGS). CAPOTEN may be used as initial therapy for patients with normal renal function, in whom the risk is relatively low. In patients with impaired renal function, particularly those with collagen vascular disease, captopril should be reserved for those who have either developed unacceptable side effects on other drugs, or have failed to respond satisfactorily to drug combinations. CAPOTEN is effective alone and in combination with other antihypertensive agents, especially thiazide-type diuretics.

Heart Failure: CAPOTEN (captopril) is indicated in patients with heart failure who have not responded adequately to or cannot be controlled by conventional diuretic and digitalis therapy. CAPOTEN is to be used with diuretics and digitalis.

CONTRAINDICATIONS: CAPOTEN is contraindicated in patients who are hypersensitive to this product.

WARNINGS: Neutropenia/Agranulocytosis – Neutropenia (< 1000/mm³) with myeloid hypoplasia has resulted from use of captopril. About half of the neutropenic patients developed systemic or oral cavity infections or other features of the syndrome of agranulocytosis. The risk of neutropenia is dependent on the clinical status of the patient:

In clinical trials in patients with hypertension who have normal renal function (serum creatinine less than 1.6 mg/dL and no collagen vascular disease), neutropenia has been seen in one patient out of over 8,600 exposed. In patients with some degree of renal failure (serum creatinine at least 1.6 mg/dL) but no collagen vascular disease, the risk in clinical trials was about 1 per 500. Doses were relatively high in these patients, particularly in view of their diminished renal function. In patients with collagen vascular diseases (e.g., systemic lupus erythematosus, scleroderma) and impaired renal function, neutropenia occurred in 3.7% of patients in clinical trials. While none of the over 750 patients in formal clinical trials of heart failure developed neutropenia, it has occurred during the subsequent clinical experience. Of reported cases, about half had serum creatinine ≥ 1.6 mg/dL and more than 75% received procainamide. In heart failure, it appears that the same risk factors for neutropenia are present.

Neutropenia has appeared usually within 3 months after starting therapy, associated with myeloid hypoplasia and frequently accompanied by erythroid hypoplasia and decreased numbers of megakaryocytes (e.g., hypoplastic bone marrow and pancytopenia); anemia and thrombocytopenia were sometimes seen. Neutrophils generally returned to normal in about 2 weeks after captopril was discontinued, and serious infections were limited to clinically complex patients. About 13% of the cases of neutropenia have ended fatally, but almost all fatalities were in patients with serious illness, having collagen vascular disease, renal failure, heart failure or immunosuppressant therapy, or a combination of these complicating factors. **Evaluation of the hypertensive or heart failure patient should always include assessment of renal function.** If captopril is used in patients with impaired renal function, white blood cell and differential counts should be evaluated prior to starting treatment and at approximately 2-week intervals for about 3 months, then periodically. In patients with collagen vascular disease or who are exposed to other drugs known to affect the white cells or immune response, particularly when there is impaired renal function, captopril should be used only after an assessment of benefit and risk, and then with caution. All patients treated with captopril should be told to report any signs of infection (e.g., sore throat, fever). If infection is suspected, perform white cell counts without delay. Since discontinuation of captopril and other drugs has generally led to prompt return of the white count to normal, upon confirmation of neutropenia (neutrophil count < 1000/mm³) withdraw captopril and closely follow the patient's course.

Proteinuria: Total urinary proteins ≥ 1 g per day were seen in about 0.7% of patients on captopril. About 90% of affected patients had evidence of prior renal disease or received high doses (> 150 mg/day), or both. The nephrotic syndrome occurred in about one-fifth of proteinuric patients. In most cases, proteinuria subsided or cleared within 6 months whether or not captopril was continued. The BUN and creatinine were seldom altered in proteinuric patients. Since most cases of proteinuria occurred by the 8th month of therapy with captopril, patients with prior renal disease or those receiving captopril at doses > 150 mg per day, should have urinary protein estimates (dip-stick on 1st morning urine) before therapy, and periodically thereafter.

Hypotension: Excessive hypotension was rarely seen in hypertensive patients but is a possibility in severely salt/volume-depleted persons such as those treated vigorously with diuretics (see PRECAUTIONS [Drug Interactions]). In heart failure, where the blood pressure was either normal or low, transient decreases in mean blood pressure > 20% were recorded in about half of the patients. This transient hypotension may occur after any of the first several doses and is usually well tolerated, although rarely it has been associated with arrhythmia or conduction defects. A starting dose of 6.25 or 12.5 mg tid may minimize the hypotensive effect. Patients should be followed closely for the first 2 weeks of treatment and whenever the dose of captopril and/or diuretic is increased.

BECAUSE OF THE POTENTIAL FALL IN BLOOD PRESSURE IN THESE PATIENTS, THERAPY SHOULD BE STARTED UNDER VERY CLOSE MEDICAL SUPERVISION.

PRECAUTIONS: General: *Impaired Renal Function* – Hypertension – Some hypertensive patients with renal disease, particularly those with severe renal artery stenosis, have developed increases in BUN and serum creatinine. It may be necessary to reduce captopril dosage and/or discontinue diuretic. For some of these patients, normalization of blood pressure and maintenance of adequate renal perfusion may not be possible. Heart Failure – About 20% of patients develop stable elevations of BUN and serum creatinine > 20% above normal or baseline upon long-term treatment. Less than 5% of patients, generally with severe preexisting renal disease, required discontinuation due to progressively increasing creatinine. See DOSAGE AND ADMINISTRATION, ADVERSE REACTIONS [Altered Laboratory Findings]. *Valvular Stenosis* – A theoretical concern, for risk of decreased coronary perfusion, has been noted regarding vasodilator treatment in patients with aortic stenosis due to decreased afterload reduction. *Surgery/Anesthesia* – If hypotension occurs during surgery or anesthesia, and is considered due to the effects of captopril, it is correctable by volume expansion.

Drug Interactions: *Hypotension – Patients on Diuretic Therapy* – Precipitous reduction of blood pressure may occasionally occur within the 1st hour after administration of the initial of captopril dose in patients on diuretics, especially those recently placed on diuretics, and those on severe dietary salt restriction or dialysis. This possibility can be minimized by either discontinuing the diuretic or increasing the salt intake about 1 week prior to initiation of captopril therapy or by initiating therapy with small doses (6.25 or 12.5 mg). Alternatively, provide medical supervision for at least 1 hour after the initial dose.

Agents Having Vasodilator Activity – In heart failure patients, vasodilators should be administered with caution.

Agents Causing Renin Release – Captopril's effect will be augmented by antihypertensive agents that cause renin release.

Agents Affecting Sympathetic Activity – The sympathetic nervous system may be especially important in supporting blood pressure in patients receiving captopril alone or with diuretics. Beta-adrenergic blocking drugs add some further antihypertensive effect to captopril, but the overall response is less than additive. Therefore, use agents affecting sympathetic activity (e.g., ganglionic blocking agents or adrenergic neuron blocking agents) with caution.

Agents Increasing Serum Potassium – Give potassium-sparing diuretics or potassium supplements only for documented hypokalemia, and then with caution, since they may lead to a significant increase of serum potassium. Use potassium-containing salt substitutes with caution.

Inhibitors of Endogenous Prostaglandin Synthesis – Indomethacin and other nonsteroidal anti-inflammatory agents may reduce the antihypertensive effect of captopril, especially in low renin hypertension.

Drug/Laboratory Test Interaction: Captopril may cause a false-positive urine test for acetone.

Carcinogenesis, Mutagenesis and Impairment of Fertility: Two-year studies with doses of 50 to 1350 mg/kg/day in mice and rats failed to show any evidence of carcinogenic potential. Studies in rats have revealed no impairment of fertility.

Pregnancy: Category C: There are no adequate and well-controlled studies in pregnant women. Embryocidal effects and craniofacial malformations were observed in rabbits. Therefore, captopril should be used during pregnancy, or for patients likely to become pregnant, only if the potential benefit outweighs the potential risk to the fetus. Captopril crosses the human placenta.

Nursing Mothers: Captopril is secreted in human milk. Exercise caution when administering captopril to a nursing woman, and, in general, nursing should be interrupted.

Pediatric Use: Safety and effectiveness in children have not been established although there is limited experience with use of captopril in children from 2 months to 15 years of age. Dosage, on a weight basis, was comparable to that used in adults. CAPOTEN (captopril) should be used in children only if other measures for controlling blood pressure have not been effective.

ADVERSE REACTIONS: Reported incidences are based on clinical trials involving approximately 7000 patients.

Renal – About 1 of 100 patients developed proteinuria (see WARNINGS). Renal insufficiency, renal failure, polyuria, oliguria, and urinary frequency in 1 to 2 of 1000 patients.

Hematologic – Neutropenia/agranulocytosis has occurred (see WARNINGS). Anemia, thrombocytopenia, and pancytopenia have been reported.

Dermatologic – Rash, (usually maculopapular, rarely urticarial), often with pruritus, and sometimes with fever and eosinophilia, in about 4 to 7 of 100 patients (depending on renal status and dose), usually during the 1st 4 weeks of therapy. Pruritus, without rash, in about 2 of 100 patients. A reversible associated pemphigoid-like lesion, and photosensitivity, have also been reported. Angioedema of the face, mucous membranes of the mouth, or of the extremities in about 1 of 1000 patients – reversible on discontinuance of captopril therapy. One case of laryngeal edema has been reported. Flushing or pallor in 2 to 5 of 1000 patients.

Cardiovascular – Hypotension may occur; see WARNINGS and PRECAUTIONS [Drug Interactions] for discussion of hypotension on initiation of captopril therapy. Tachycardia, chest pain, and palpitations each in about 1 of 100 patients. Angina pectoris, myocardial infarction, Raynaud's syndrome, and congestive heart failure each in 2 to 3 of 1000 patients.

Dysgeusia – Approximately 2 to 4 (depending on renal status and dose) of 100 patients developed a diminution or loss of taste perception; taste impairment is reversible and usually self-limited even with continued drug use (2 to 3 months). Gastric irritation, abdominal pain, nausea, vomiting, diarrhea, anorexia, constipation, aphthous ulcers, peptic ulcer, dizziness, headache, malaise, fatigue, insomnia, dry mouth, dyspnea, cough, alopecia, paresthesias reported in about 0.5 to 2% of patients but did not appear at increased frequency compared to placebo or other treatments used in controlled trials.

Altered Laboratory Findings: Elevations of liver enzymes in a few patients although no causal relationship has been established. Rarely cholestatic jaundice, and hepatocellular injury with or without secondary cholestasis, have been reported. A transient elevation of BUN and serum creatinine may occur, especially in volume-depleted or renovascular hypertension patients. In instances of rapid reduction of longstanding or severely elevated blood pressure, the glomerular filtration rate may decrease transiently, also resulting in transient rises in serum creatinine and BUN. Small increases in serum potassium concentration frequently occur, especially in patients with renal impairment (see PRECAUTIONS).

OVERDOSAGE: Primary concern is correction of hypotension. Volume expansion with an I.V. infusion of normal saline is the treatment of choice for restoration of blood pressure. Captopril may be removed from the general circulation by hemodialysis.

DOSAGE AND ADMINISTRATION: CAPOTEN (captopril) should be taken one hour before meals. In hypertension, CAPOTEN may be dosed bid or tid. Dosage must be individualized; see DOSAGE AND ADMINISTRATION section of package insert for detailed information regarding dosage in hypertension and in heart failure. Because CAPOTEN (captopril) is excreted primarily by the kidneys, dosage adjustments are recommended for patients with impaired renal function.

Consult package insert before prescribing CAPOTEN (captopril).

HOW SUPPLIED: Available in tablets of 12.5, 25, 50, and 100 mg in bottles of 100 (25 mg and 50 mg also available in bottles of 1000), and in UNIMATIC® unit-dose packs of 100 tablets. (J3-658J)

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Authors are urged to seek clarity and succinctness in all manuscripts regardless of subject matter or format and to give close attention to syntax, grammar, and spelling.

Clinical Investigation Section

Articles that authors wish to have considered for the Clinical Investigation section should be so designated in the transmittal letter. The type of articles appropriate for this section are those that describe experimental work in humans that extensively and prospectively examines scientific hypotheses relating to disease. An article describing a single case report will not normally be considered appropriate for this section.

Preparing Manuscripts

The original manuscript and *two* copies should be submitted on heavy bond paper (8½ by 11 inches, *not* erasable), typed *double-spaced throughout* (including legends, tables, and references) on one side of the paper, with 1½-inch margins. Articles should not exceed 3,000 words (less than 15 text pages typed double-spaced). Under exceptional circumstances only will articles longer than 4,000 words be published. Pages should be numbered consecutively, beginning with the title page. Manuscripts produced with a dot-matrix printer are ordinarily not acceptable.

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Tables and Figures

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Note handling of multiple authorship. If more than three authors are listed as contributors, use "et al" to designate those names after the first three. Also note capitalization, punctuation, use of inclusive page numbers, and year of publication. Separate the subtitle from the title by either a dash or a colon. Use colon *only* if it appears in the original citation.

1. Jones JS, Anderson HW, Johnson DW, et al: The athletic heart revisited—Sudden death of a 28-year-old athlete. JAMA 1978; 292:444-456

2. Graybill JR, Alford RH, Smith RG, et al: Cell-mediated immunity in cryptococcosis: A brief review. Cell Immunol 1978; 7:76-79

Books

Note handling of "edition," "editor(s)," and "volume," as well as appropriate sequence of reference information and capitalization of chapters and titles.

3. Berne EJ, Smith TL: Role playing in therapy, chap 2, Principles of Group Therapy. New York, Oxford University Press, 1966, pp 35-51 *(author of chapter same as author of book)*

4. Munsung JM: The role of drugs, chap 2, *In* Brest AN, Mayer JH (Eds): Hypertension—Vol 2, Therapy, 2nd Ed. Springfield, Ill, Charles C Thomas, 1961, pp 456-479 *(author of chapter different from authors of book)*

Pamphlets, Monographs, or Books With No Given Author

5. AMA Department of Drugs: AMA Drug Evaluation, 3rd Ed. Littleton, Mass, Publishing Sciences Group, 1977 *(corporate author)*

6. Compilation of Standard Definitions, 3rd Ed. Philadelphia, American Society for Testing and Materials, 1976 *(no given author; give name and place of publisher)*

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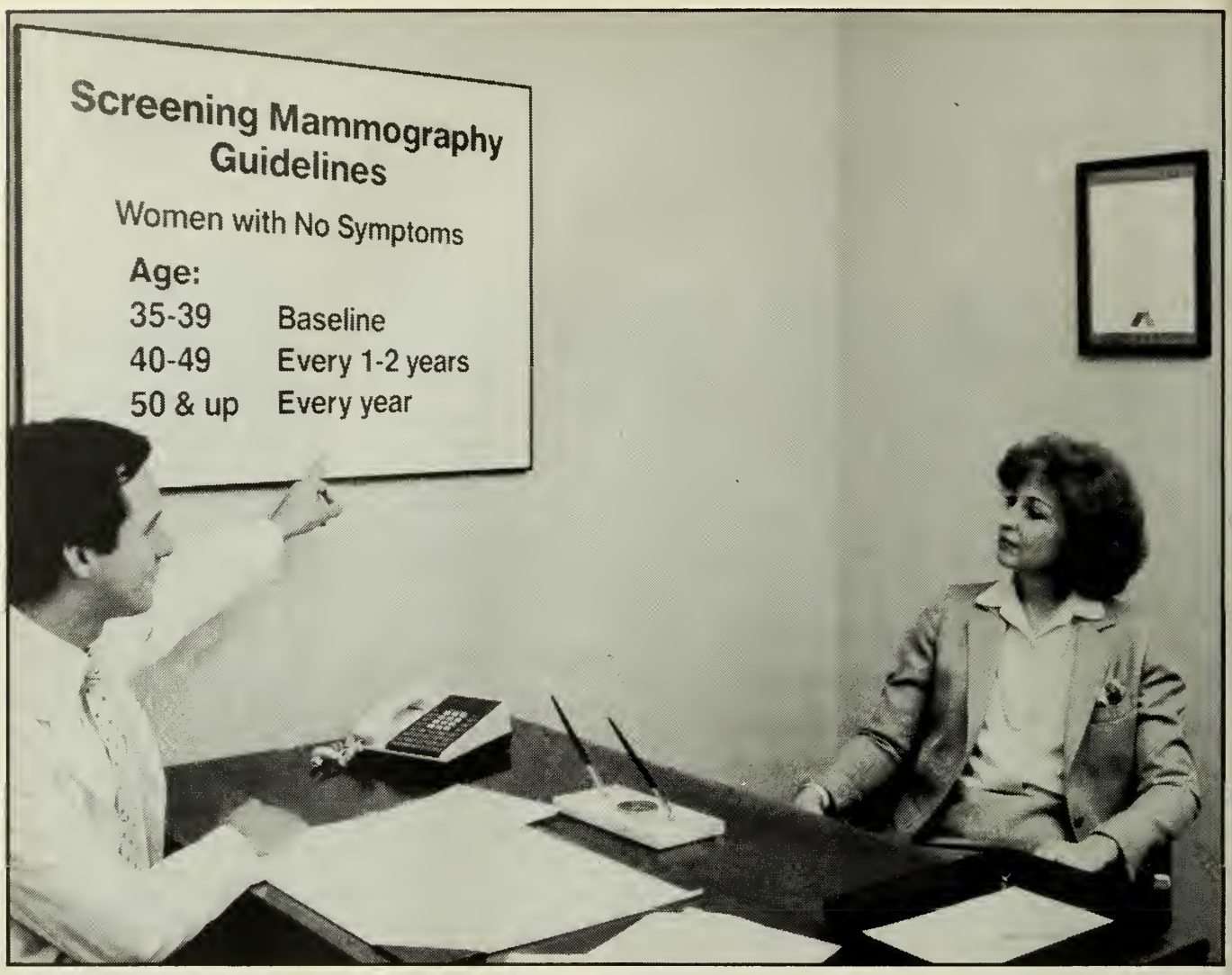

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†See Warnings and Precautions.

Please see brief summary of prescribing information on the next page.

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(diltiazem HCl) 30 mg, 60 mg, 90 mg, and 120 mg Tablets

CONTRAINDICATIONS
CARDIZEM is contraindicated in (1) patients with sick sinus syndrome except in the presence of a functioning ventricular pacemaker, (2) patients with second- or third-degree AV block except in the presence of a functioning ventricular pacemaker, and (3) patients with hypotension (less than 90 mm Hg systolic).

WARNINGS
1. **Cardiac Conduction.** CARDIZEM prolongs AV node refractory periods without significantly prolonging sinus node recovery time, except in patients with sick sinus syndrome. This effect may rarely result in abnormally slow heart rates (particularly in patients with sick sinus syndrome) or second- or third-degree AV block (six of 1,243 patients for 0.48%). Concomitant use of diltiazem with beta-blockers or digitalis may result in additive effects on cardiac conduction. A patient with Prinzmetal's angina developed periods of asystole (2 to 5 seconds) after a single dose of 60 mg of diltiazem.
2. **Congestive Heart Failure.** Although diltiazem has a negative inotropic effect in isolated animal tissue preparations, hemodynamic studies in humans with normal ventricular function have not shown a reduction in cardiac index nor consistent negative effects on contractility (dp/dt).
Experience with the use of CARDIZEM alone or in combination with beta-blockers in patients with impaired ventricular function is very limited. Caution should be exercised when using the drug in such patients.
3. **Hypotension.** Decreases in blood pressure associated with CARDIZEM therapy may occasionally result in symptomatic hypotension.
4. **Acute Hepatic Injury.** In rare instances, significant elevations in enzymes such as alkaline phosphatase, CPK, LDH, SGOT, SGPT, and other symptoms consistent with acute hepatic injury have been noted. These reactions have been reversible upon discontinuation of drug therapy. The relationship to CARDIZEM is uncertain in most cases, but probable in some. (See PRECAUTIONS.)

PRECAUTIONS
General. CARDIZEM (diltiazem hydrochloride) is extensively metabolized by the liver and excreted by the kidneys and in bile. As with any new drug given over prolonged periods, laboratory parameters should be monitored at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function. In subacute and chronic dog and rat studies designed to produce toxicity, high doses of diltiazem were associated with hepatic damage. In special subacute hepatic studies, oral doses of 125 mg/kg and higher in rats were associated with histological changes in the liver which were reversible when the drug was discontinued. In dogs, doses of 20 mg/kg were also associated with hepatic changes; however, these changes were reversible with continued dosing.
Drug Interaction. Pharmacologic studies indicate that there may be additive effects in prolonging AV conduction when using beta-blockers or digitalis concomitantly with CARDIZEM. (See WARNINGS.)
Controlled and uncontrolled domestic studies suggest that concomitant use of CARDIZEM and beta-blockers or digitalis is usually well tolerated. Available data are not sufficient, however, to predict the effects of concomitant treatment, particularly in patients with left ventricular dysfunction or cardiac conduction abnormalities. In healthy volunteers, diltiazem has been shown to increase serum digoxin levels up to 20%.
Carcinogenesis, Mutagenesis, Impairment of Fertility. A 24-month study in rats and a 21-month study in mice showed no evidence of carcinogenicity. There was also no mutagenic response in in vitro bacterial tests. No intrinsic effect on fertility was observed in rats.
Pregnancy. Category C. Reproduction studies have been conducted in mice, rats, and rabbits. Administration of doses ranging from five to ten times greater (on a mg/kg basis) than the daily recommended therapeutic dose has resulted in embryo and fetal lethality. These doses, in some studies, have been reported to cause skeletal abnormalities. In the perinatal/postnatal studies, there was some reduction in early individual pup weights and survival rates. There was an increased incidence of stillbirths at doses of 20 times the human dose or greater.
There are no well-controlled studies in pregnant women; therefore, use CARDIZEM in pregnant women only if the potential benefit justifies the potential risk to the fetus.
Nursing Mothers. Diltiazem is excreted in human milk. One report suggests that concentrations in breast milk may approximate serum levels. If use of CARDIZEM is deemed essential, an alternative method of infant feeding should be instituted.
Pediatric Use. Safety and effectiveness in children have not been established.

ADVERSE REACTIONS
Serious adverse reactions have been rare in studies carried out to date, but it should be recognized that patients with impaired ventricular function and cardiac conduction abnormalities have usually been excluded.
In domestic placebo-controlled trials, the incidence of adverse reactions reported during CARDIZEM therapy was not greater than that reported during placebo therapy.
The following represent occurrences observed in clinical studies which can be at least reasonably associated with the pharmacology of calcium influx inhibition. In many cases, the relationship to CARDIZEM has not been established. The most common occurrences as well as their frequency of presentation are: edema (2.4%), headache (2.1%), nausea (1.9%), dizziness (1.5%), rash (1.3%), asthenia (1.2%). In addition, the following events were reported infrequently (less than 1%).

Cardiovascular:	Angina, arrhythmia, AV block (first degree), AV block (second or third degree — see conduction warning), bradycardia, congestive heart failure, flushing, hypotension, palpitations, syncope.
Nervous System:	Amnesia, gait abnormality, hallucinations, insomnia, nervousness, paresthesia, personality change, somnolence, tinnitus, tremor.
Gastrointestinal:	Anorexia, constipation, diarrhea, dysgeusia, dyspepsia, mild elevations of alkaline phosphatase, SGOT, SGPT, and LDH (see hepatic warnings), vomiting, weight increase.
Dermatologic:	Petechiae, pruritus, photosensitivity, urticaria.
Other:	Amblyopia, dyspnea, epistaxis, eye irritation, hyperglycemia, nasal congestion, nocturia, osteoarticular pain, polyuria, sexual difficulties.

The following postmarketing events have been reported infrequently in patients receiving CARDIZEM: alopecia, gingival hyperplasia, erythema multiforme, and leukopenia. However, a definitive cause and effect between these events and CARDIZEM therapy is yet to be established.

Issued 9/86

See complete Professional Use Information before prescribing.

References: 1. Schroeder JS: Mod Med 1982;50(Sept):94-116. **2.** Cohn PF, Braunwald E: Chronic ischemic heart disease, in Braunwald E (ed): Heart Disease: A Textbook of Cardiovascular Medicine, ed 2. Philadelphia, WB Saunders Co, 1984, chap 39. **3.** O'Rourke RA: Am J Cardiol 1985;56:34H-40H. **4.** McCall D, Walsh RA, Frohlich ED, et al: Curr Probl Cardiol 1985;10(8):6-80. **5.** Frishman WH, Charlop S, Goldberger J, et al: Am J Cardiol 1985;56:41H-46H. **6.** Shapiro W: Consultant 1984;24(Dec):150-159. **7.** O'Hara MJ, Khurmi NS, Bowles MJ, et al: Am J Cardiol 1984;54:477-481. **8.** Strauss WE, McIntyre KM, Parisi AF, et al: Am J Cardiol 1982;49:560-566. **9.** Feldman RL, Pepine CJ, Whiffle J, et al: Am J Cardiol 1982;49:554-559.

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ARIZONA

The following list of continuing medical education programs in Arizona is compiled by the Arizona Medical Association. All courses listed have been certified as meeting the criteria for Category I of the ArMA CME Certificate and the AMA Physicians Recognition Award. To list Category I continuing medical education programs, please send information to Arizona Medical Association, 810 West Bethany Home Road, Phoenix, AZ 85013; or phone (602) 246-8901.

Brochures and registration forms are available from the contact person or organization sponsoring the program.

February 20—**A Practical Approach to Management II** (Diabetes Conference). Crescent Hotel, Phoenix. Sat. Contact: Good Samaritan Medical Center, Byron Woodson, (602) 239-5994 or 1 (800) 443-5972 (within Arizona).

February 25-27—**Contraception, Sterilization, and Sexually Transmitted Disease.** Paradise Valley Resort, Scottsdale. Thurs-Sat. Contact: Robin Murray, American College of Obstetricians and Gynecologists, (202) 863-2543.

February 25-27—**Them Ol' Bones V.** Scottsdale Sheraton Resort, Scottsdale. Thurs-Sat. Contact: Christine Campbell for St Luke's Medical Center, (602) 838-6728.

February 25-28—**Arizona Academy of Family Physicians Scientific Assembly—1988.** Embassy Suites—The Biltmore, Phoenix. Thurs-Sun. Contact: AAFP, (602) 249-2021.

February 26-28—**Fourteenth Annual Scientific Session of the Arizona Society of Anesthesiologists.** Scottsdale Hilton Resort, Scottsdale. Fri-Sun. Contact: Beverly Richter, Arizona Society of Anesthesiologists, (602) 246-8901.

February 29-March 3—**Practical Radiology.** Loews Ventana Canyon Resort, Tucson. Mon-Thurs. Contact: U of A.

March 2-4—**11th Annual Mid-Winter Symposium in OB/GYN.** Scottsdale Hilton Hotel, Scottsdale. Wed-Fri. Contact: Secretary, Phoenix OB/GYN Society, (602) 241-1917.

March 5—**Current Perspectives: Cancer Screening, Treatment and Follow up.** Arizona Medical Association, Phoenix. Sat. Contact: ArMA.

March 6-9—**2nd Annual Barrow Neurological Institute Magnetic Resonance Imaging Conference.** Camelback Inn Resort, Scottsdale. Sun-Wed. Contact: Barrow Neurological Institute, (602) 285-3178 or 1 (800) BARROW-1

March 10-12—**Practical Cardiology for the Family Physician.** La Posada Resort Hotel, Scottsdale. Thurs-Sat. Contact: American College of Cardiology, (800) 253-4636, ext 226.

March 10-12—**15th Annual Symposium: Selected Topics in Ischemic and Hemorrhagic Cerebrovascular Disease.** Camelback Inn Resort, Scottsdale. Thurs-Sat. Contact: Barrow Neurological Institute, (602) 285-3178 or 1 (800) BARROW-1.

March 17-19—**24th Annual Arizona Chest Symposium.** Doubletree Hotel, Tucson. Thurs-Sat. Contact: Susan Thornton, RN, MS, Tucson Medical Center, (602) 327-5461, Ext. 5110.

March 22-25—**Pediatric Update 1988.** La Posada Resort Hotel, Scottsdale. Tues-Fri. Contact: Paul C. Stillwell, MD, Phoenix Children's Hospital, (602) 239-5778.

March 23-27—**12th Annual Valley of the Sun Dermatologic Symposium.** Stouffers Cottonwoods Resort, Scottsdale. Wed-Sun. Contact: Phoenix Dermatologic Society, c/o Susan Slama, MD, (602) 991-3203.

CONTACT INFORMATION

ArMA—Contact: Arizona Medical Association, 810 W Bethany Home Rd, Phoenix, AZ 85013. (602) 246-8901.

U of A—Contact: University of Arizona College of Medicine, Arizona Health Sciences Center, Tucson, AZ 85724. (602) 626-6707.

PATHOLOGY

May 14-15—**Selected Topics in Gynecologic Pathology.** Arizona Society of Pathologists and U of A at Westward Look Resort, Tucson. Sat-Sun. 7 hrs. Contact: Beverly Richter, Arizona Society of Pathologists, 810 W Bethany Home Rd, Phoenix 85013. (602) 246-8901.

CALIFORNIA, HAWAII AND NEVADA

This listing of continuing education programs in California, Hawaii and Nevada is supplied by the Committee on Continuing Medical Education of the California Medical Association. All courses and meetings listed have been approved for Category I credit toward the CMA Certificate in Continuing Medical Education. To have accredited courses listed here, please send information at least two months in advance to Department of Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690; or phone (415) 863-5522. For a list of organizations approved for Category I credit toward the CMA Certificate in Continuing Medical Education or for more information on accreditation or certification, please write to the above address.

KEY TO ABBREVIATIONS

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690. (415) 863-5522.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Herbert M. Thomas, MD, MPH, Director of CME, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th Street, Los Angeles 90059. (213) 603-3183.

LLU: Loma Linda University
Contact: Varner J. Johns, Jr, MD, Associate Dean for Continuing Medical Education, Loma Linda University School of Medicine, Loma Linda 92354. (714) 796-7311, ext 2400.

PMC: Pacific Medical Center
Contact: Continuing Education, Pacific Medical Center, PO Box 7999, San Francisco 94120. (415) 563-4321, ext 2761.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Medical School Office Building, Suite X-365, Stanford 94305-6114. (415) 723-5594.

UCD: University of California, Davis
Contact: Ruth Feryok, Director, Office of Continuing Medical Education, University of California, Davis, School of Medicine, 2701 Stockton Boulevard, Sacramento 95817. (916) 453-5390.

UCI: University of California, Irvine
Contact: Melvin I. Marks, MD, Assistant Dean, University of California, Irvine, California College of Medicine, c/o UCI/CME Program, Memorial Medical Center, 2801 Atlantic Avenue, Long Beach 90801-1428. (213) 595-3811, or (714) 856-5414, UCI Extension.

UCLA: University of California, Los Angeles
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, PO Box 24902, UCLA, Los Angeles 90024. (213) 825-7241.

UCSD: University of California, San Diego
Contact: Office of Continuing Medical Education, University of California, San Diego, School of Medicine (M-017), La Jolla 92093. (619) 534-3713.

UCSF: University of California, San Francisco
Contact: Robert Maggio, Administrative Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 476-4251.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 1975 Zonal Ave, KAM314, Los Angeles 90033. (213) 224-7051.

(Continued on Page 158)

The World's Most Popular K*

Slow-K®

potassium chloride
slow-release tablets
8 mEq (600 mg)

It means "dependability" in almost any language

*Based on worldwide sales data on file, CIBA Pharmaceutical Company.
Capsule or tablet slow-release potassium chloride preparations should be reserved for patients who cannot tolerate, refuse to take, or have compliance problems with liquid or effervescent potassium preparations because of reports of intestinal and gastric ulceration and bleeding with slow-release KCl preparations.

Before prescribing, please consult Brief Prescribing Information on next page.

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- ☐ **It's comparable to 10 mEq**—in low-dosage supplementation[3]†
- ☐ **It's economical**—less expensive than all other leading KCl slow-release supplements on a per tablet cost to the patient[1]

Slow-K®
potassium chloride
slow-release tablets 8 mEq (600 mg)

For patients who can't or won't tolerate liquid KCl.

*The most common adverse reactions to potassium salts are gastrointestinal side effects.

†Pooled mean serum potassium following oral administration of 30 mEq K-Tab compared to 24 mEq Slow-K in diuretic-treated hypertensives (n = 20) over 8 weeks.

C I B A

References: 1. Data on file, CIBA Pharmaceutical Company. **2.** Skoutakis VA, Acchiardo SR, Wojciechowski NJ, et al: Liquid and solid potassium chloride: Bioavailability and safety. *Pharmacotherapy* 1980;4(6):392-397. **3.** Skoutakis VA, Carter CA, Acchiardo SR: Therapeutic assessment of Slow-K and K-Tab potassium chloride formulations in hypertensive patients treated with thiazide diuretics. *Drug Intell Clin Pharm* 1987;21:436-440.

Slow-K®
potassium chloride USP
Slow-Release Tablets
8 mEq (600 mg)

BRIEF SUMMARY (FOR FULL PRESCRIBING INFORMATION SEE PACKAGE INSERT)

INDICATIONS AND USAGE

BECAUSE OF REPORTS OF INTESTINAL AND GASTRIC ULCERATION AND BLEEDING WITH SLOW-RELEASE POTASSIUM CHLORIDE PREPARATIONS, THESE DRUGS SHOULD BE RESERVED FOR THOSE PATIENTS WHO CANNOT TOLERATE OR REFUSE TO TAKE LIQUID OR EFFERVESCENT POTASSIUM PREPARATIONS OR FOR PATIENTS IN WHOM THERE IS A PROBLEM OF COMPLIANCE WITH THESE PREPARATIONS.

1. For therapeutic use in patients with hypokalemia with or without metabolic alkalosis; in digitalis intoxication and in patients with hypokalemic familial periodic paralysis.
2. For prevention of potassium depletion when the dietary intake of potassium is inadequate in the following conditions: patients receiving digitalis and diuretics for congestive heart failure; hepatic cirrhosis with ascites; states of aldosterone excess with normal renal function; potassium-losing nephropathy; and certain diarrheal states.
3. The use of potassium salts in patients receiving diuretics for uncomplicated essential hypertension is often unnecessary when such patients have a normal dietary pattern. Serum potassium should be checked periodically, however, and if hypokalemia occurs, dietary supplementation with potassium-containing foods may be adequate to control milder cases. In more severe cases supplementation with potassium salts may be indicated.

CONTRAINDICATIONS

Potassium supplements are contraindicated in patients with hyperkalemia, since a further increase in serum potassium concentration in such patients can produce cardiac arrest. Hyperkalemia may complicate any of the following conditions: chronic renal failure, systemic acidosis such as diabetic acidosis, acute dehydration, extensive tissue breakdown as in severe burns, adrenal insufficiency, or the administration of a potassium-sparing diuretic (e.g., spironolactone, triamterene) (see OVERDOSAGE).

All solid dosage forms of potassium supplements are contraindicated in any patient in whom there is cause for arrest or delay in tablet passage through the gastrointestinal tract. In these instances, potassium supplementation should be with a liquid preparation. Wax-matrix potassium chloride preparations have produced esophageal ulceration in certain cardiac patients with esophageal compression due to an enlarged left atrium.

WARNINGS

Hyperkalemia (See OVERDOSAGE).

In patients with impaired mechanisms for excreting potassium, the administration of potassium salts can produce hyperkalemia and cardiac arrest. This occurs most commonly in patients given potassium by the intravenous route but may also occur in patients given potassium orally. Potentially fatal hyperkalemia can develop rapidly and be asymptomatic.

The use of potassium salts in patients with chronic renal disease, or any other condition which impairs potassium excretion, requires particularly careful monitoring of the serum potassium concentration and appropriate dosage adjustment.

Interaction With Potassium-Sparing Diuretics

Hyperkalemia should not be treated by the concomitant administration of potassium salts and a potassium-sparing diuretic (e.g., spironolactone or triamterene), since the simultaneous administration of these agents can produce severe hyperkalemia.

Gastrointestinal Lesions

Potassium chloride tablets have produced stenotic and/or ulcerative lesions of the small bowel and deaths. These lesions are caused by a high localized concentration of potassium ion in the region of a rapidly dissolving tablet, which injures the bowel wall and thereby produces obstruction, hemorrhage, or perforation. Slow-K is a wax-matrix tablet formulated to provide a controlled rate of release of potassium chloride and thus to minimize the possibility of a high local concentration of potassium ion near the bowel wall. While the reported frequency of small-bowel lesions is much less with wax-matrix tablets (less than one per 100,000 patient-years) than with enteric-coated potassium chloride tablets (40-50 per 100,000 patient-years) cases associated with wax-matrix tablets have been reported both in foreign countries and in the United States. In addition, perhaps because the wax-matrix preparations are not enteric-coated and release potassium in the stomach, there have been reports of upper gastrointestinal bleeding associated with these products. The total number of gastrointestinal lesions remains approximately one per 100,000 patient-years. Slow-K should be discontinued immediately and the possibility of bowel obstruction or perforation considered if severe vomiting, abdominal pain, distention, or gastrointestinal bleeding occurs.

Metabolic Acidosis

Hypokalemia in patients with metabolic acidosis should be treated with an alkalinizing potassium salt such as potassium bicarbonate, potassium citrate, or potassium acetate.

PRECAUTIONS

General:

The diagnosis of potassium depletion is ordinarily made by demonstrating hypokalemia in a patient with a clinical history suggesting some cause for potassium depletion. In interpreting the serum potassium level, the physician should bear in mind that acute alkalosis *per se* can produce hypokalemia in the absence of a deficit in total body potassium, while acute acidosis *per se* can increase the serum potassium concentration into the normal range even in the presence of a reduced total body potassium.

Information for Patients

Physicians should consider reminding the patient of the following:

To take each dose without crushing, chewing, or sucking the tablets.

To take this medicine only as directed. This is especially important if the patient is also taking both diuretics and digitalis preparations.

To check with the physician if there is trouble swallowing tablets or if the tablets seem to stick in the throat.

To check with the doctor at once if tarry stools or other evidence of gastrointestinal bleeding is noticed.

Laboratory Tests

Regular serum potassium determinations are recommended. In addition, during the treatment of potassium depletion, careful attention should be paid to acid-base balance, other serum electrolyte levels, the electrocardiogram, and the clinical status of the patient, particularly in the presence of cardiac disease, renal disease, or acidosis.

Drug Interactions

Potassium-sparing diuretics: see WARNINGS.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term carcinogenicity studies in animals have not been performed.

Pregnancy Category C

Animal reproduction studies have not been conducted with Slow-K. It is also not known whether Slow-K can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Slow-K should be given to a pregnant woman only if clearly needed.

Nursing Mothers

The normal potassium ion content of human milk is about 13 mEq/L. It is not known if Slow-K has an effect on this content. Caution should be exercised when Slow-K is administered to a nursing woman.

Pediatric Use

Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

One of the most severe adverse effects is hyperkalemia (see CONTRAINDICATIONS, WARNINGS, and OVERDOSAGE). There also have been reports of upper and lower gastrointestinal conditions including obstruction, bleeding, ulceration, and perforation (see CONTRAINDICATIONS and WARNINGS); other factors known to be associated with such conditions were present in many of these patients.

The most common adverse reactions to oral potassium salts are nausea, vomiting, abdominal discomfort, and diarrhea. These symptoms are due to irritation of the gastrointestinal tract and are best managed by taking the dose with meals or reducing the dose.

Skin rash has been reported rarely.

OVERDOSAGE

The administration of oral potassium salts to persons with normal excretory mechanisms for potassium rarely causes serious hyperkalemia. However, if excretory mechanisms are impaired or if potassium is administered too rapidly intravenously, potentially fatal hyperkalemia can result (see CONTRAINDICATIONS and WARNINGS). It is important to recognize that hyperkalemia is usually asymptomatic and may be manifested only by an increased serum potassium concentration (6.5-8.0 mEq/L) and characteristic electrocardiographic changes (peaking of T waves, loss of P wave, depression of S-T segment, and prolongation of the Q-T interval). Late manifestations include muscle paralysis and cardiovascular collapse from cardiac arrest (9-12 mEq/L).

Treatment measures for hyperkalemia include the following: (1) elimination of foods and medications containing potassium and of potassium-sparing diuretics; (2) intravenous administration of 300-500 ml/hr of 10% dextrose solution containing 10-20 units of insulin per 1,000 ml; (3) correction of acidosis, if present, with intravenous sodium bicarbonate; (4) use of exchange resins, hemodialysis, or peritoneal dialysis.

In treating hyperkalemia in patients who have been stabilized on digitalis, too rapid a lowering of the serum potassium concentration can produce digitalis toxicity.

DOSAGE AND ADMINISTRATION

The usual dietary intake of potassium by the average adult is 40-80 mEq per day. Potassium depletion sufficient to cause hypokalemia usually requires the loss of 200 or more mEq of potassium from the total body store. Dosage must be adjusted to the individual needs of each patient but is typically in the range of 20 mEq per day for the prevention of hypokalemia to 40-100 mEq or more per day for the treatment of potassium depletion. Large numbers of tablets should be given in divided doses.

Note: Slow-K slow-release tablets must be swallowed whole and never crushed, chewed, or sucked.

HOW SUPPLIED

Tablets—600 mg of potassium chloride (equivalent to 8 mEq) round, buff colored, sugar-coated (imprinted Slow-K)

Bottles of 100	NDC 0083-0165-30
Bottles of 1000	NDC 0083-0165-40
Consumer Pack—One Unit	
12 Bottles—100 tablets each	NDC 0083-0165-65
Accu-Pak® Unit Dose (Blister pack)	
Box of 100 (strips of 10)	NDC 0083-0165-32

Do not store above 86°F (30°C). Protect from moisture. Protect from light.

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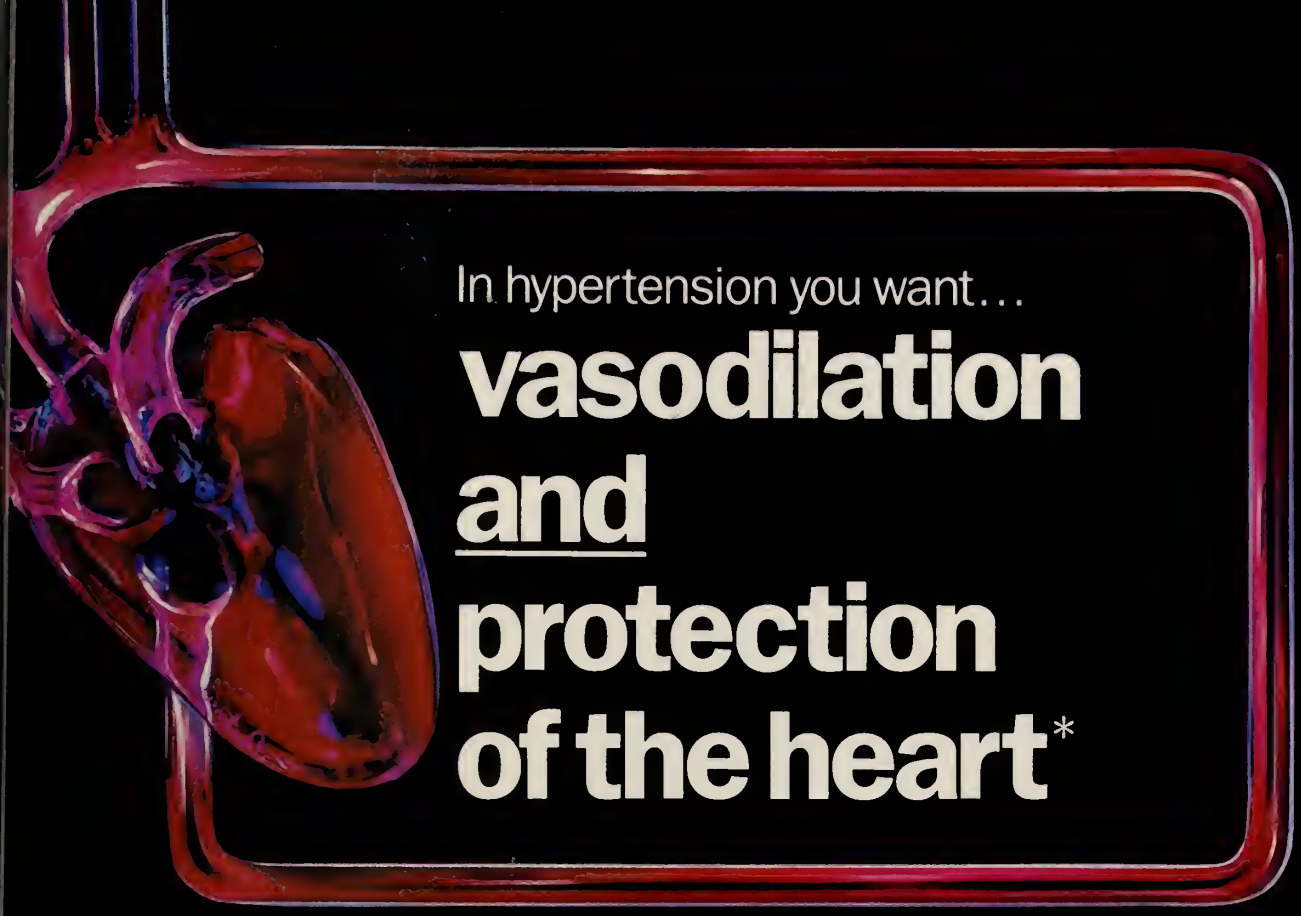

NORMODYNE® gives you both

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	vasodilation	beta blockade
NORMODYNE (labetalol HCl) Tablets	✓	✓
Beta Blockers		✓
ACE Inhibitors	✓	
Calcium Channel Blockers	✓	

- ☐ Low incidence of impotence, fatigue, or cold extremities†
- ☐ Lipid and potassium levels are not adversely affected
- ☐ Minimizes risk of reflex tachycardia
- ☐ Maintains cardiac output
- ☐ Maintains exercise capacity
- ☐ Does not adversely affect heart rate
- ☐ Maintains blood flow to vital organs
- ☐ Renal function is unimpaired

educes double product (HR × SBP) and minimizes the risk of reflex tachycardia
Most adverse effects are mild, transient, and occur early in the course of treatment. In controlled clinical trials of three to four months' duration, the most common side effects noted in treating mild to moderate hypertension with NORMODYNE (labetalol HCl) Tablets include dizziness (11%), nausea (6%), and fatigue (5%). Dyspepsia (3%), nasal stuffiness (3%), impotence (1%), and drowsiness (<1%) occurred to a lesser degree. Overall, reports of symptomatic postural hypotension have been uncommon and have included rare instances of syncope. For complete side effects profile, see Prescribing Information.

For Brief Summary, please see reverse side of page.

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PRODUCT INFORMATION

NORMODYNE®

brand of labetalol hydrochloride

Tablets

BRIEF SUMMARY

INDICATIONS AND USAGE

NORMODYNE (labetalol HCl) Tablets are indicated in the management of hypertension. NORMODYNE Tablets may be used alone or in combination with other antihypertensive agents, especially thiazide and loop diuretics.

CONTRAINDICATIONS

NORMODYNE (labetalol HCl) Tablets are contraindicated in bronchial asthma, overt cardiac failure, greater than first degree heart block, cardiogenic shock, and severe bradycardia (see **WARNINGS**).

WARNINGS

Cardiac Failure Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure. Beta blockade carries a potential hazard of further depressing myocardial contractility and precipitating more severe failure. Although beta-blockers should be avoided in overt congestive heart failure, if necessary, labetalol HCl can be used with caution in patients with a history of heart failure who are well-compensated. Congestive heart failure has been observed in patients receiving labetalol HCl. Labetalol HCl does not abolish the inotropic action of digitalis on heart muscle.

In Patients Without a History of Cardiac Failure In patients with latent cardiac insufficiency, continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or be given a diuretic, and the response observed closely. If cardiac failure continues, despite adequate digitalization and diuretic, NORMODYNE (labetalol HCl) therapy should be withdrawn (gradually if possible).

Exacerbation of Ischemic Heart Disease Following Abrupt Withdrawal Angina pectoris has not been reported upon labetalol HCl discontinuation. However, hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy; exacerbation of angina and, in some cases, myocardial infarction have occurred after *abrupt* discontinuation of such therapy. When discontinuing chronically administered NORMODYNE (labetalol HCl), particularly in patients with ischemic heart disease, the dosage should be gradually reduced over a period of one to two weeks and the patient should be carefully monitored. If angina markedly worsens or acute coronary insufficiency develops, NORMODYNE (labetalol HCl) administration should be reinstituted promptly, at least temporarily, and other measures appropriate for the management of unstable angina should be taken. Patients should be warned against interruption or discontinuation of therapy without the physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue NORMODYNE (labetalol HCl) therapy abruptly even in patients treated only for hypertension.

Nonallergic Bronchospasm (e.g., chronic bronchitis and emphysema) Patients with bronchospastic disease should, in general, not receive beta-blockers. NORMODYNE may be used with caution, however, in patients who do not respond to, or cannot tolerate, other antihypertensive agents. It is prudent, if NORMODYNE is used, to use the smallest effective dose, so that inhibition of endogenous or exogenous beta-agonists is minimized.

Pheochromocytoma Labetalol HCl has been shown to be effective in lowering the blood pressure and relieving symptoms in patients with pheochromocytoma. However, paradoxical hypertensive responses have been reported in a few patients with this tumor; therefore, use caution when administering labetalol HCl to patients with pheochromocytoma.

Diabetes Mellitus and Hypoglycemia Beta-adrenergic blockade may prevent the appearance of premonitory signs and symptoms (e.g., tachycardia) of acute hypoglycemia. This is especially important with labile diabetics. Beta-blockade also reduces the release of insulin in response to hyperglycemia; it may therefore be necessary to adjust the dose of antidiabetic drugs.

Major Surgery The necessity or desirability of withdrawing beta-blocking therapy prior to major surgery is controversial. Protracted severe hypotension and difficulty in restarting or maintaining a heart beat have been reported with beta-blockers. The effect of labetalol HCl's alpha-adrenergic activity has not been evaluated in this setting.

A synergism between labetalol HCl and halothane anesthesia has been shown (see **Drug Interactions**).

PRECAUTIONS

General *Impaired Hepatic Function* NORMODYNE (labetalol HCl) Tablets should be used with caution in patients with impaired hepatic function since metabolism of the drug may be diminished.

Jaundice or Hepatic Dysfunction On rare occasions, labetalol HCl has been associated with jaundice (both hepatic and cholestatic). It is therefore recommended that treatment with labetalol HCl be stopped immediately should a patient develop jaundice or laboratory evidence of liver injury. Both have been shown to be reversible on stopping therapy.

Information for Patients

As with all drugs with beta-blocking activity, certain advice to patients being treated with labetalol HCl is warranted. This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects. While no incident of the abrupt withdrawal phenomenon (exacerbation of angina pectoris) has been reported with labetalol HCl, dosing with NORMODYNE Tablets should not be interrupted or discontinued without a physician's advice. Patients being treated with NORMODYNE Tablets should consult a physician at any sign of impending cardiac failure. Also, transient scalp tingling may occur, usually when treatment with NORMODYNE Tablets is initiated (see **ADVERSE REACTIONS**).

Laboratory Tests

As with any new drug given over prolonged periods, laboratory parameters should be observed over regular intervals. In patients with concomitant illnesses, such as impaired renal function, appropriate tests should be done to monitor these conditions.

Drug Interactions

In one survey, 2.3% of patients taking labetalol HCl in combination with tricyclic antidepressants experienced tremor as compared to 0.7% reported to occur with labetalol HCl alone. The contribution of each of the treatments to this adverse reaction is unknown but the possibility of a drug interaction cannot be excluded.

Drugs possessing beta-blocking properties can blunt the bronchodilator effect of beta-receptor agonist drugs in patients with bronchospasm; therefore, doses greater than the normal anti-asthmatic dose of beta-agonist bronchodilator drugs may be required.

Cimetidine has been shown to increase the bioavailability of labetalol HCl. Since this could be explained either by enhanced absorption or by an alteration of hepatic metabolism of labetalol HCl, special care should be used in establishing the dose required for blood pressure control in such patients.

Synergism has been shown between halothane anesthesia and intravenously administered labetalol HCl. During controlled hypotensive anesthesia using labetalol HCl in association with halothane, high concentrations (3% or above) of halothane should not be used because the degree of hypotension will be increased and because of the possibility of a large reduction in cardiac output and an increase in central venous pressure. The anesthesiologist should be informed when a patient is receiving labetalol HCl.

Labetalol HCl blunts the reflex tachycardia produced by nitroglycerin without preventing its hypotensive effect. If labetalol HCl is used with nitroglycerin in patients with angina pectoris, additional antihypertensive effects may occur.

Drug/Laboratory Test Interactions

The presence of a metabolite of labetalol in the urine may result in falsely increased levels of urinary catecholamines when measured by a nonspecific trihydroxyindole (THI) reaction. In screening patients suspected of having a pheochromocytoma and being treated with labetalol HCl, specific radioenzymatic or high performance liquid chromatography assay techniques should be used to determine levels of catecholamines or their metabolites.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term oral dosing studies with labetalol HCl for 18 months in mice and for 2 years in rats showed no evidence of carcinogenesis. Studies with labetalol HCl, using dominant lethal assays in rats and mice, and exposing microorganisms according to modified Ames tests, showed no evidence of mutagenesis.

Pregnancy Category C

Teratogenic studies have been performed with labetalol in rats and rabbits at oral doses up to approximately 6 and 4 times the maximum recommended human dose (MRHD), respectively. No reproducible evidence of fetal malformations was observed. Increased fetal resorptions were seen in both species at doses approximating the MRHD. There are no adequate and well-controlled studies in pregnant women. Labetalol should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects

Infants of mothers who were treated with labetalol HCl for hypertension during pregnancy did not appear to be adversely affected by the drug. Oral administration of labetalol to rats during late gestation through weaning at doses of 2 to 4 times the MRHD caused a decrease in neonatal survival.

Labor and Delivery

Labetalol HCl given to pregnant women with hypertension did not appear to affect the usual course of labor and delivery.

Nursing Mothers

Small amounts of labetalol (approximately 0.004% of the maternal dose) are excreted in human milk. Caution should be exercised when NORMODYNE Tablets are administered to a nursing woman.

Pediatric Use

Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Most adverse effects are mild, transient and occur early in the course of treatment. In controlled clinical trials of 3 to 4 months duration, discontinuation of NORMODYNE (labetalol HCl) Tablets due to one or more adverse effects was required in 7% of all patients. In these same trials, beta-blocker control agents led to discontinuation in 8 to 10% of patients, and a centrally acting alpha-agonist in 30% of patients.

The incidence rates of adverse reactions listed in the following table were derived from multicenter controlled clinical trials, comparing labetalol HCl, placebo, metoprolol and propranolol, over treatment periods of 3 and 4 months. Where the frequency of adverse effects for labetalol HCl and placebo is similar, causal relationship is uncertain. The rates are based on adverse reactions considered probably drug-related by the investigator. If all reports are considered, the rates are somewhat higher (e.g., dizziness 20%, nausea 14%, fatigue 11%), but the overall conclusions are unchanged.

	Labetalol HCl (N=227) %	Placebo (N=98) %	Propranolol (N=84) %	Metoprolol (N=49) %
Body as a whole				
fatigue	5	0	12	12
asthenia	1	1	1	0
headache	2	1	1	2
Gastrointestinal				
nausea	6	1	1	2
vomiting	<1	0	0	0
dyspepsia	3	1	1	0
abdominal pain	0	0	1	2
diarrhea	<1	0	2	0
taste distortion	1	0	0	0
Central and Peripheral Nervous Systems				
dizziness	11	3	4	4
paresthesias	<1	0	0	0
drowsiness	<1	2	2	2
Autonomic Nervous System				
nasal stuffiness	3	0	0	0
ejaculation failure	2	0	0	0
impotence	1	0	1	3
increased sweating	<1	0	0	0
Cardiovascular				
edema	1	0	0	0
postural hypotension	1	0	0	0
bradycardia	0	0	5	12
Respiratory				
dyspnea	2	0	1	2
Skin				
rash	1	0	0	0
Special Senses				
vision abnormality	1	0	0	0
vertigo	2	1	0	0

The adverse effects were reported spontaneously and are representative of the incidence of adverse effects that may be observed in a properly selected hypertensive patient population, i.e., a group excluding patients with bronchospastic disease, overt congestive heart failure, or other contraindications to beta-blocker therapy.

Clinical trials also included studies utilizing daily doses up to 2400 mg in more severely hypertensive patients. Certain of the side effects increased with increasing dose as shown in the table below which depicts the entire U.S. therapeutic trials data base for adverse reactions that are clearly or possibly dose related.

Labetalol HCl Daily Dose (mg)	200	300	400	600
Number of Patients	522	181	606	608
Dizziness (%)	2	3	3	3
Fatigue	2	1	4	4
Nausea	<1	0	1	2
Vomiting	0	0	<1	<1
Dyspepsia	1	0	2	1
Paresthesias	2	0	2	2
Nasal Stuffiness	1	1	2	2
Ejaculation Failure	0	2	1	2
Impotence	1	1	1	1
Edema	1	0	1	1

Labetalol HCl Daily Dose (mg)	800	900	1200	1600	2400
Number of Patients	503	117	411	242	175
Dizziness (%)	5	1	9	13	16
Fatigue	5	3	7	6	10
Nausea	4	0	7	11	19
Vomiting	<1	0	1	2	3
Dyspepsia	1	0	2	2	4

Labetalol HCl Daily Dose (mg) (cont.)	800	900	1200	1600	2400
Paresthesias	1	1	2	5	5
Nasal Stuffiness	2	2	4	5	6
Ejaculation Failure	3	0	4	3	5
Impotence	2	4	3	4	3
Edema	1	0	1	2	2

In addition, a number of other less common adverse events have been reported in clinical trials or the literature:

Cardiovascular Postural hypotension, including rarely, syncope.

Central and Peripheral Nervous Systems Paresthesias, most frequently described as scalp tingling. In most cases, it was mild, transient and usually occurred at the beginning of treatment.

Collagen Disorders Systemic lupus erythematosus; positive antinuclear factor (ANF).

Eyes Dry eyes.

Immunological System Antimitochondrial antibodies.

Liver and Biliary System Cholestasis with or without jaundice.

Musculo-Skeletal System Muscle cramps; toxic myopathy.

Respiratory System Bronchospasm.

Skin and Appendages Rashes of various types, such as generalized maculo-papular; lichenoid; urticanal; bullous lichen planus; psoriaform; facial erythema; Peyronie's disease; reversible alopecia.

Urinary System Difficulty in micturition, including acute urinary bladder retention.

Following approval for marketing in the United Kingdom, a monitored release survey involving approximately 6,800 patients was conducted for further safety and efficacy evaluation of this product. Results of this survey indicate that the type, severity, and incidence of adverse effects were comparable to those cited above.

Potential Adverse Effects

In addition, other adverse effects not listed above have been reported with other beta-adrenergic blocking agents.

Central Nervous System Reversible mental depression progressing to catatonia; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Cardiovascular Intensification of AV block. See **CONTRAINDICATIONS.**

Allergic Fever combined with aching and sore throat; laryngospasm; respiratory distress.

Hematologic Agranulocytosis; thrombocytopenic or nonthrombocytopenic purpura.

Gastrointestinal Mesenteric artery thrombosis; ischemic colitis.

The oculomucocutaneous syndrome associated with the beta-blocker practolol has not been reported with labetalol HCl.

Clinical laboratory tests: There have been reversible increases of serum transaminases in 4% of patients treated with labetalol HCl and tested, and more rarely, reversible increases in blood urea.

OVERDOSAGE

Overdosage with NORMODYNE (labetalol HCl) Tablets causes excessive hypotension which is posture sensitive, and sometimes, excessive bradycardia. Patients should be laid supine and their legs raised if necessary to improve the blood supply to the brain. The following additional measures should be employed if necessary: *Excessive bradycardia* — administer atropine (3.0 mg). If there is no response to vagal blockade, administer isoproterenol cautiously. *Cardiac failure* — administer a digitalis glycoside and a diuretic. *Hypotension* — administer vasopressors, e.g., norepinephrine. There is pharmacological evidence that norepinephrine may be the drug of choice. *Bronchospasm* — administer a beta$_2$-stimulating agent and/or a theophylline preparation.

Gastric lavage or pharmacologically induced emesis (using syrup of ipecac) is useful for removal of the drug shortly after ingestion. Labetalol HCl can be removed from the general circulation by hemodialysis.

The oral LD_{50} value of labetalol HCl in the mouse is approximately 600 mg/kg and in the rat is greater than 2 gm/kg. The intravenous LD_{50} in these species is 50 to 60 mg/kg.

DOSAGE AND ADMINISTRATION

DOSAGE MUST BE INDIVIDUALIZED. The recommended initial dose is 100 mg twice daily whether used alone or added to a diuretic regimen. After 2 or 3 days, using standing blood pressure as an indicator, dosage may be titrated in increments of 100 mg bid every 2 or 3 days. The usual maintenance dosage of labetalol HCl is between 200 and 400 mg twice daily.

Since the full antihypertensive effect of labetalol HCl is usually seen within the first one to three hours of the initial dose or dose increment, the assurance of a lack of an exaggerated hypotensive response can be clinically established in the office setting. The antihypertensive effects of continued dosing can be measured at subsequent visits, approximately 12 hours after a dose, to determine whether further titration is necessary.

Patients with severe hypertension may require from 1200 mg to 2400 mg per day, with or without thiazide diuretics. Should side effects (principally nausea or dizziness) occur with these doses administered bid, the same total daily dose administered three times daily may improve tolerability and facilitate further titration. Titration increments should not exceed 200 mg twice daily.

When a diuretic is added, an additive antihypertensive effect can be expected. In some cases this may necessitate a labetalol HCl dosage adjustment. As with most antihypertensive drugs, optimal dosages of NORMODYNE Tablets are usually lower in patients also receiving a diuretic.

When transferring patients from other antihypertensive drugs, NORMODYNE Tablets should be introduced as recommended and the dosage of the existing therapy progressively decreased.

HOW SUPPLIED

NORMODYNE (labetalol HCl) Tablets, 100 mg, light-brown, round, scored, film-coated tablets engraved on one side with Schering and product identification numbers 244, and on the other side the number 100 for the strength and "NORMODYNE"; bottles of 100 (NDC-0085-0244-04), 500 (NDC-0085-0244-05), and box of 100 for unit-dose dispensing (NDC-0085-0244-08).

NORMODYNE (labetalol HCl) Tablets, 200 mg, white, round, scored, film-coated tablets engraved on one side with Schering and product identification numbers 752, and on the other side the number 200 for the strength and "NORMODYNE"; bottles of 100 (NDC-0085-0752-04), 500 (NDC-0085-0752-05), box of 100 for unit-dose dispensing (NDC-0085-0752-08), and Patient Calendar Package of 56 (4 bottles of 14 tablets) (NDC-0085-0752-03).

NORMODYNE (labetalol HCl) Tablets, 300 mg, blue, round, film-coated tablets engraved on one side with Schering and product identification numbers 438, and on the other side the number 300 for the strength and "NORMODYNE"; bottles of 100 (NDC-0085-0438-03), 500 (NDC-0085-0438-05), box of 100 for unit-dose dispensing (NDC-0085-0438-06), and Patient Calendar Package of 56 (4 bottles of 14 tablets) (NDC-0085-0438-02).

NORMODYNE (labetalol HCl) Tablets should be stored between 2° and 30°C (36° and 86°F).

NORMODYNE (labetalol HCl) Tablets in the unit-dose boxes should be protected from excessive moisture.

For complete prescribing information, please consult package insert.

Key Pharmaceuticals, Inc
Kenilworth, NJ 07033 USA

Revised 3/85

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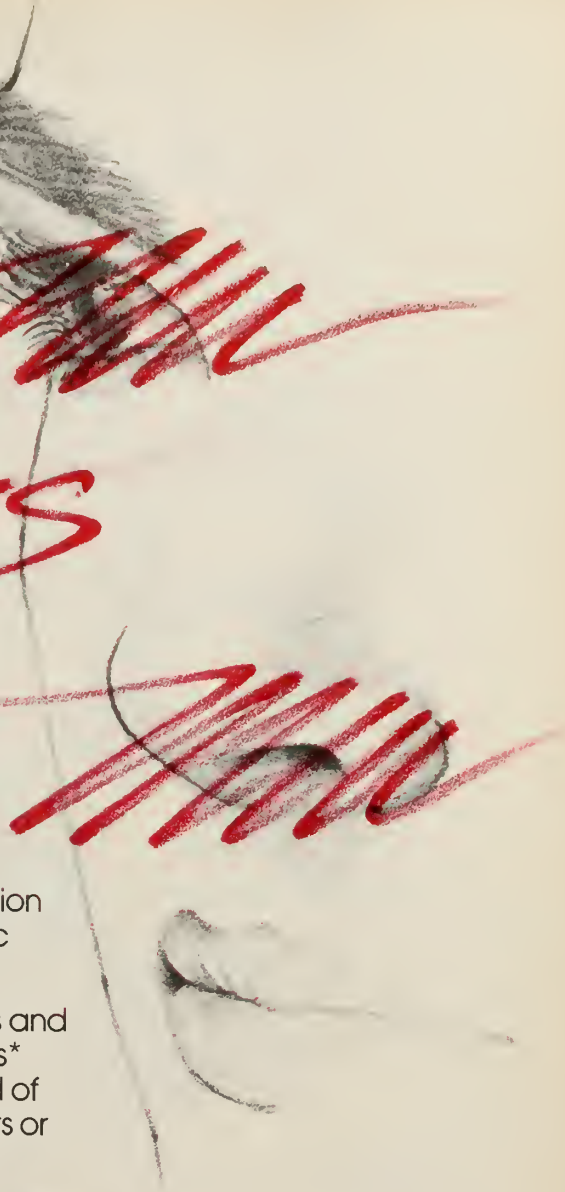
NR-613/14315403

DON'T OVERLOOK THE EYES WHEN TREATING ALLERGIES



More than 8 out of 10 patients who present with allergic rhinitis may suffer from concurrent allergic ocular signs and symptoms —itchy, scratchy eyes, erythema and edema, tearing, irritation—according to two recent studies.[1,2]

What's worse is that many patients don't mention their ocular symptoms when reporting allergic rhinitis unless specifically asked.

So look for the overlapping clinical symptoms and then confidently treat allergic ocular disorders* with OPTICROM. It has a proven clinical record of efficacy with freedom from serious side effects or ocular toxicity.

OPHTHALMIC SOLUTION

OPTICROM® 4%

(cromolyn sodium, USP)

THE SOLUTION FOR ALLERGIC OCULAR DISORDERS*

Reference 1,2 Data on file, Fisons Corporation
Independent Studies by DTW Market Research Group July 1985

*See below for listing of certain allergic ocular disorders

INDICATIONS AND USAGE: OPTICROM is indicated in the treatment of certain allergic ocular disorders referred to by the terms vernal keratoconjunctivitis, vernal conjunctivitis, giant papillary conjunctivitis, vernal keratitis, and allergic keratoconjunctivitis. The etiologic factors are unknown, but common airborne allergens and contact lenses have been implicated.[1]

Symptomatic response to therapy (decreased itching, tearing, redness, and discharge) is usually evident within a few days, but longer treatment for up to six weeks is sometimes required. Once symptomatic improvement has been established, therapy should be continued for as long as needed to sustain improvement.

If required, corticosteroids may be used concomitantly with OPTICROM.

Users of soft (hydrophilic) contact lenses should refrain from wearing lenses while under treatment with OPTICROM (see **Contraindications**). Wear can be resumed within a few hours after discontinuation of the drug.

CONTRAINDICATIONS: OPTICROM is contraindicated in those patients who have shown hypersensitivity to cromolyn sodium or to any of the other ingredients.

As with all ophthalmic preparations containing benzalkonium chloride, patients are advised not to wear soft contact lenses during treatment with OPTICROM.

PRECAUTIONS: General: Patients may experience a transient stinging or burning sensation following application of OPTICROM.

The recommended frequency of administration should not be exceeded. The dose for adults and children is 1-2 drops in each eye 4-6 times a day at regular intervals.

Carcinogenesis, Mutagenesis, and Impairment of Fertility: Long term studies in mice (12 months intraperitoneal treatment followed by six months observation), hamsters (12 months intraperitoneal treatment followed by 12 months observation), and rats (18 months subcutaneous treatment) showed no neoplastic effect of cromolyn sodium.

No evidence of chromosomal damage or cytotoxicity was obtained in various mutagenesis studies.

No evidence of impaired fertility was shown in laboratory animal reproduction studies.

Pregnancy: Pregnancy Category B. Reproduction studies with cromolyn sodium administered parenterally to pregnant mice, rats and rabbits in doses up to 338 times the human clinical doses produced no evidence of fetal malformations. Adverse fetal effects (increased resorption and decreased fetal weight) were noted only at the very high parenteral doses that produced maternal toxicity. There are, however, no adequate and well controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when OPTICROM is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in children below the age of 4 years have not been established.

ADVERSE REACTIONS: The most frequently reported adverse reaction attributed to the use of OPTICROM, on the basis of reoccurrence following readministration, is transient ocular stinging or burning upon instillation.

The following adverse reactions have been reported as infrequent events. It is unclear whether they are attributable to the drug: conjunctival injection, watery eyes, itchy eyes, dryness around the eye, puffy eyes, eye irritation, styes.

CAUTION: Federal law prohibits dispensing without prescription.

REFERENCE: 1. Allansmith MR, Abelson MB. Ocular Allergies. In: *The Cornea*, ed. by G. Smolin, RA Thoft, Little, Brown and Co., Boston/Toronto, 1983: 231-43.

See package insert for full prescribing information.

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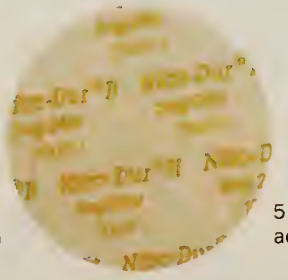
Nitro-Dur® II
(nitroglycerin)
Transdermal Infusion System

Easy to open... apply... remove.



5 mg patch, actual size.

Please see next page for brief summary of prescribing information.

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Nitro-Dur® II
(nitroglycerin)
Transdermal Infusion System

- Easy opening—even for arthritic hands.
- Round-the-clock cling—lies flat, holds tight.
- Hard to notice, easy to wear—semitransparent, soft and flexible.
- Push-button removal—just a press in the center raises the rim for easy lift-off.

When prescribing Nitro-Dur II, you should write your prescription using the Roman numeral designation II to identify the product. This should be followed by the appropriate dosage strength in mg/24 hours. Thus, any confusion that may arise between product names and/or dosage strengths prescribed will be avoided.

BRIEF SUMMARY

INDICATIONS AND USAGE: This drug product has been conditionally approved by the FDA for the prevention and treatment of angina pectoris due to coronary artery disease. The conditional approval reflects a determination that the drug may be marketed while further investigation of its effectiveness is undertaken. A final evaluation of the effectiveness of the product will be announced by the FDA.

CONTRAINDICATIONS: Intolerance of organic nitrate drugs, marked anemia

WARNINGS: The NITRO-DUR II system should be used under careful clinical and/or hemodynamic monitoring in patients with acute myocardial infarction or congestive heart failure.

In terminating treatment of anginal patients, both the dosage and frequency of application must be gradually reduced over a period of 4 to 6 weeks in order to prevent sudden withdrawal reactions, which are characteristic of all vasodilators in the nitroglycerin class.

PRECAUTIONS: Symptoms of hypotension, such as faintness, weakness or dizziness, particularly orthostatic hypotension, may be due to overdosage. If during the course of treatment these symptoms occur, the dosage should be reduced or use of the product discontinued. NITRO-DUR II is not intended for use in the treatment of acute anginal attacks. For this purpose, occasional use of sublingual nitroglycerin may be necessary.

Pregnancy: Pregnancy Category C. Animal reproduction studies have not been conducted with NITRO-DUR II. It is also not known whether nitroglycerin can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Nitroglycerin should be given to a pregnant woman only if clearly needed.

Nursing Mothers: It is not known whether nitroglycerin is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when NITRO-DUR II is administered to a nursing woman.

ADVERSE REACTIONS: Transient headache is the most common side effect, especially when higher doses of the drug are administered. Headaches should be treated with mild analgesics while continuing NITRO-DUR II therapy. If headache persists, the NITRO-DUR II dosage should be reduced or use of the product discontinued.

Adverse reactions reported less frequently include hypotension, increased heart rate, faintness, flushing, dizziness, nausea, vomiting, and dermatitis. Except for dermatitis, these symptoms are attributed to the pharmacologic effects of nitroglycerin. However, they may be symptoms of overdosage. When they persist, the NITRO-DUR II dosage should be reduced or use of the product discontinued.

CAUTION: Federal law prohibits dispensing without prescription. For complete prescribing information, please see package insert.

EDP #I030150 Revised 0585

All transdermal nitroglycerin products are being marketed pending final evaluation of effectiveness by the FDA.

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ND-2101 14440402

In Memoriam

Arizona Medical Association

Bernstein, Dennis, Tucson. Died Nov 6, 1987, aged 75. Graduate of State University of New York College of Medicine, 1937. Licensed in Arizona in 1946. Dr Bernstein was a member of the Pima County Medical Society.

Hirsch, Louis, Tucson. Died Dec 8, 1987, aged 73. Graduate of New York University School of Medicine, New York, 1937. Licensed in Arizona in 1947. Dr Hirsch was a member of the Pima County Medical Society.

Kiser, David M., Prescott. Died Nov 7, 1987, aged 62. Graduate of University of Kansas School of Medicine, Kansas City. Licensed in Arizona in 1968. Dr Kiser was a member of the Yavapai County Medical Society.

Likos, Joseph J., Phoenix. Died Oct 12, 1987, aged 68. Graduate of St Louis University School of Medicine, 1945. Licensed in Arizona in 1955. Dr Likos was a member of the Maricopa County Medical Society.

Lustgarten, Earl M., Scottsdale. Died Oct 12, 1987, aged 84. Graduate of University of Illinois College of Medicine, Chicago, 1931. Licensed in Arizona in 1978. Dr Lustgarten was a member of the Maricopa County Medical Society.

Mackoff, Sam M., Phoenix. Died Dec 16, 1987, aged 73. Graduate of University of Minnesota Medical School, 1944. Licensed in Arizona in 1955. Dr Mackoff was a member of the Maricopa County Medical Society.

Rosenthal, Maurice, Phoenix. Died Oct 2, 1987, aged 84. Graduate of Medical College of Virginia School of Medicine, Richmond, 1926. Licensed in Arizona in 1943. Dr Rosenthal was a member of the Maricopa County Medical Society.

Toland, Virgil A., Phoenix. Died Oct 22, 1987, aged 76. Graduate of Creighton University School of Medicine, Omaha, 1936. Licensed in California in 1944. Dr Toland was a member of the Maricopa County Medical Society.

Tomlinson, Walter B., Elgin. Died Oct 25, 1987, aged 72. Graduate of Northwestern University Medical School, Chicago, 1946. Licensed in Arizona in 1973. Dr Tomlinson was a member of the Santa Cruz County Medical Society.

California Medical Association

Hoiland, Dean, Paradise. Died Oct 18, 1987, aged 68. Graduate of Loma Linda University, 1944. Licensed in California in 1944. Dr Hoiland was a member of the Butte-Glenn Medical Society.

Hoskins, H. Dean, Oakland. Died Sep 17, 1987, aged 74. Graduate of Stanford University School of Medicine, 1942. Licensed in California in 1944. Dr Hoskins was amember of the Alameda-Contra Costa Medical Association.

Stark, James A., Oakland. Died Sep 9, 1987, aged 73. Graduate of University of California, San Francisco, 1940. Licensed in California in 1940. Dr Stark was a member of the Alameda-Contra Costa Medical Association.

Taw, Richard. Died Sep 1, 1987, aged 72. Graduate of University of Southern California, Los Angeles, 1943. Licensed in California in 1943. Dr Taw was a member of the Los Angeles County Medical Association.

New Mexico Medical Society

Adler, Stuart W., Fullerton, California. Died Dec 1987, aged 95. Graduate of Harvard Medical School, Boston, 1919. Licensed in New Mexico in 1933. Dr Adler was a retired member of the Greater Albuquerque Medical Association.

WHY AMA?

The AMA provides a democratic forum where you, along with your colleagues across the country, can raise and argue issues, reach a consensus and formulate policy. AMA policy is then translated into practical actions on issues that affect you and your practice. Making sure medicine stays active, strong and united: it's one more good reason why you should be a part of the AMA.

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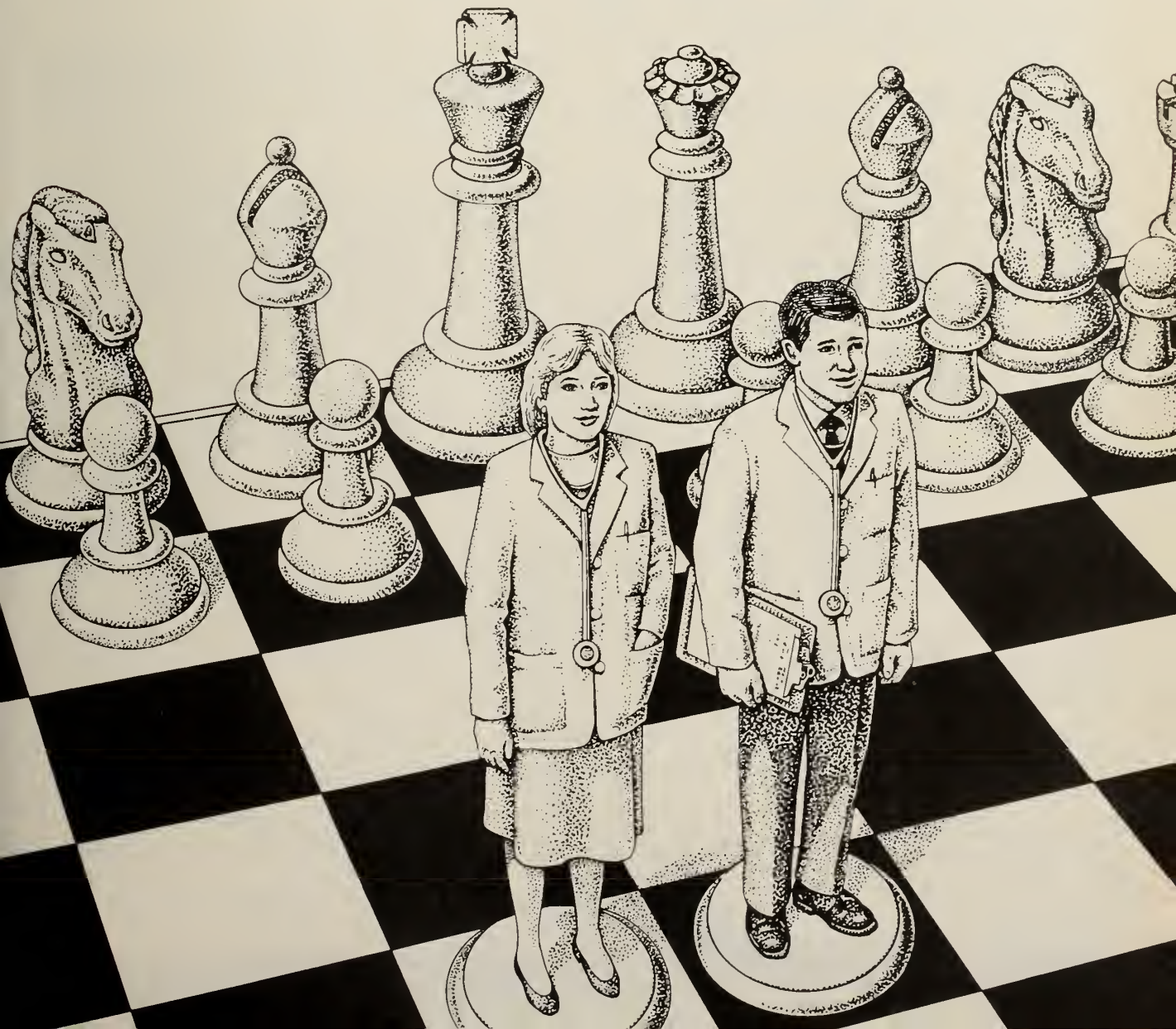

CONTINUING MEDICAL EDUCATION

(Continued from Page 148)

ALLERGY

February 23-28—**Intermediate Course in Otolaryngic Allergy and Immunology.** American Academy of Otolaryngic Allergy Foundation at Miyako Hotel, San Francisco. Tues-Sun. 30 hrs. $550. Contact: American Academy of Otolaryngic Allergy, 1101 Vermont Avenue, NW, Suite 303 Washington, DC, 20005.

March 28-30—**Office and Hospital Based Clinical Nutrition for the Practitioner.** University of Washington at Maui, Hawaii. Mon-Wed. Contact: U/W School of Medicine, Div of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

ANESTHESIOLOGY

March 13-18—**Anesthesiology 1988.** Anesthesiology Educational Foundation at Mammoth Lakes, Sierra Nevada Inn. Sun-Fri. Contact: Anesthesiology Educational Foundation, PO Box 24230, Los Angeles 90024.

March 19-20—**33rd Postgraduate Assembly.** Los Angeles Society of Anesthesiologists at Los Angeles Hilton Hotel. Sat-Sun. Contact: Laura Lee, Los Angeles Society of Anesthesiologists, PO Box 3465, Los Angeles, 90051-1465. (213) 483-1581 ext. 320.

May 15-20—**Hawaiian Seminar on Clinical Anesthesia.** California Society of Anesthesiologists at Sheraton Kauai Hotel, Poipu Beach, Kauai. Sun-Fri. 20 hrs. $325-375. Contact: California Society of Anesthesiologists, 1065 Hillsdale Blvd, #410, Foster City 94404. (415) 345-3020.

May 16-20—**5th International Symposium: Computing in Anesthesia and Intensive Care.** UCSD at US Grant Hotel, San Diego. Mon-Fri. 20 hrs. $300. Contact: UCSD.

June 16-19—**California Society of Anesthesiologists 1988 Annual Meeting** at Marriott Hotel, Anaheim. Thurs-Sun. 16 hrs. $150-225. Contact: California Society of Anesthesiologists, 1065 Hillsdale Blvd, #410, Foster City 94404. (415) 345-3020.

August 21-27—**Hawaiian Seminar on Clinical Anesthesia.** California Society of Anesthesiologists at Inter-Continental Hotel, Wailea, Maui. Sun-Sat. 20 hrs. $325/$375. Contact: CSA, 1065 E. Hilldale Blvd, Suite 410, Foster City 94404. (415) 345-3020.

October 16-21—**Hawaiian Seminar on Clinical Anesthesia.** California Society of Anesthesiologists at Westin Maui Hotel, Maui. Sun-Fri. 20 hrs. $325/$375. Contact: CSA, 1065 Hilldale Blvd, Suite 410, Foster City 94404. (415) 345-3020.

CANCER

February 25-27—**Second International Conference on Intracavitary Chemotherapy.** UCSD at US Grant Hotel, San Diego. Thurs-Sat. 18 hrs. $300. Contact: UCSD.

March 12—**Ultrasound in the Diagnosis and Management of Rectal Health.** Sutter Health at Sutter General Hospital, Sacramento. Sat. 6 hrs. $45. Contact: Sutter Health, CME Dept. 2020 1 St, Suite D, Sacramento 95814. (916) 446-7681.

CARDIOLOGY

February 22-26—**Non-Invasive Diagnostic Techniques in Vascular Disease.** Scripps Clinic and Research Foundation at Sheraton Harbor Island Hotel, San Diego. Mon-Fri. 35 hrs. $550. Contact: Nomi Feldman, Conference Coordinator, 3770 Tansy St, San Diego, 92121. (619) 453-6222.

(Continued on Page 240)

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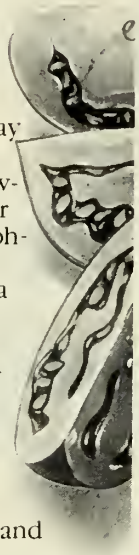

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Books Received

Books received by THE WESTERN JOURNAL OF MEDICINE *are acknowledged in this column. Selections will be made for more extensive review in the interest of readers as space permits.*

QUESTIONS & ANSWERS ON AIDS—Lyn Robert Frumkin, MD, PhD, Department of Neurology, University of California, Los Angeles, School of Medicine, and John Martin Leonard, MD, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland. Medical Economics Books, Oradell, NJ 07649, 1987. 184 pages, $19.95 (paperback).

RAISING A HANDICAPPED CHILD—A HELPFUL GUIDE FOR PARENTS OF THE PHYSICALLY DISABLED—Charlotte E. Thompson, MD, Director, Center for Handicapped Children and Teenagers, San Francisco, and Assistant Clinical Professor of Pediatrics, University of California, San Diego, Medical School. William Morrow & Company, 105 Madison Avenue, New York, NY 10016, 1986. 266 pages, $17.95.

REALITY ORIENTATION FOR THE ELDERLY—Third Edition—Sylvester Kohut, Jr, PhD, Dean, College of Education, Kutztown University, Kutztown; Jeraldine Joanne Kohut, RN, MA, Director of Nursing, Westminster Village, Allentown, Pennsylvania, and Joseph J. Fleishman, PhD, former Head Clinical Psychologist, Geriatric Psychology Program, Philadelphia State Hospital. Medical Economics Books, Oradell, NJ 07649, 1987. 149 pages, $18.95 (paperback).

REFRACTIVE KERATOPLASTY—Volume 4 in Contemporary Issues in Ophthalmology—Edited by Ivan R. Schwab, MD, Associate Professor of Ophthalmology, West Virginia University School of Medicine, Morgantown. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1987. 305 pages, $58.

ROCKY MOUNTAIN MEDICINE—Doctors, Drugs, and Disease in Early Colorado—Robert H. Shikes, MD, Vice Chairman, Department of Pathology, University of Colorado School of Medicine, Denver. Johnson Books, 1880 S 57th Court, Boulder, CO 80301, 1987. 255 pages, $34.95.

SONOGRAPHY OF THE INFANT HIP: AN ATLAS—Reinhard Graf and Peter Schuler. VCH Publishers, Inc, 220 East 23rd St, Suite 909, New York, NY 10010, 1986. 273 pages, $115.

STARTING IN MEDICAL PRACTICE—Morton Walker, DPM. Medical Economics Books, Oradell, NJ 07649, 1987. 174 pages, $22.95 (paperback).

STRANGER IN NEW MEXICO—A DOCTOR'S JOURNEY, 1951-1986—J. Peter Voute, MD. University of New Mexico Press, Albuquerque, NM 87131, 1987. 214 pages; $22.50 (cloth bound), $10.95 (paperback).

SURFACE TOPOGRAPHY AND SPINAL DEFORMITY—Proceedings of the 3rd International Symposium, September 27-28, 1984, Oxford—Edited by J. Derek Harris and Alan R. Turner-Smith. VCH Publishers, Inc, 220 E 23rd St, Suite 909, New York, NY 10010, 1986. 249 pages, $57 (paperback).

SURGERY FOR CEREBROVASCULAR DISEASE—Edited by Wesley S. Moore, MD, Professor of Surgery and Chief, Section of Vascular Surgery, UCLA School of Medicine, Los Angeles. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1987. 933 pages, $150.

SURGERY OF FACIAL BONE FRACTURES—Edited by Craig A. Foster, MD, DDS, Associate Professor of Otolaryngology and Head and Neck Surgery, New York Medical College, Valhalla; Associate Attending Surgeon (Plastic Surgery), Manhattan Eye, Ear, and Throat Hospital, and Director, Facial Plastic Surgery, New York Eye and Ear Infirmary, New York, and John E. Sherman, MD, Assistant Clinical Professor of Surgery (Plastic Surgery), Mount Sinai School of Medicine of the City University of New York; Associate Attending Surgeon, Beth Israel Medical Center, and Adjunct Attending Surgeon, Memorial Sloan-Kettering Cancer Center, New York. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1987. 273 pages, $69.

THERAPEUTIC ENDOSCOPY IN GASTROINTESTINAL SURGERY—Raphael S. Chung, MD, Professor of Surgery, State University of New York, Health Science Center at Syracuse; Director, Surgical Endoscopy Service, and Attending Surgeon, State University Hospital Veterans-Administration Medical Center and Crouse Irving Memorial Hospital, Syracuse, New York. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1987. 259 pages, $45.

TOGETHER IN THE DARK: MYSTERIES OF HEALING—Robert H. Colfelt, MD, a neurologist in private practice; Clinical Associate Professor, University of Washington, Seattle, and editor of the *King County Medical Society Bulletin*. Madrona Publishers, Inc, PO Box 22667, Seattle, WA 98122, 1987. 189 pages, $15.95.

TRAUMA—Emergency Surgery and Critical Care—Edited by John H. Siegel, MD, Professor of Surgery, University of Maryland School of Medicine; Professor of Surgery, Johns Hopkins University School of Medicine; Director, MIEMSS Clinical Center, and Deputy Director, Maryland Institute for Emergency Medical Services Systems, Baltimore. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1987. 1175 pages, $150.

WELLNESS MEDICINE—Robert A. Anderson, MD. American Health Press, PO Box 5388, Lynnwood, WA 98046-5388, 1987. 436 pages, $34.95.

ZANG FU—THE ORGAN SYSTEMS OF TRADITIONAL CHINESE MEDICINE—2ND EDITION—Jeremy Ross, CAc(Nanjing), BAc(MBAcA), BSc, CEd, MNIMH, Director, Alternative Therapies, Bristol, England. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1986. 257 pages, $46.75.

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Adverse Reactions: *Muscle cramps, weakness, dizziness, headache, dry mouth; anaphylaxis, rash, urticaria, photosensitivity, purpura, other dermatological conditions; nausea and vomiting, diarrhea, constipation, other gastrointestinal disturbances; postural hypotension (may be aggravated by alcohol, barbiturates, or narcotics). Necrotizing vasculitis, paresthesias, icterus, pancreatitis, xanthopsia and respiratory distress including pneumonitis and pulmonary edema, transient blurred vision, sialadenitis, and vertigo have occurred with thiazides alone. Triamterene has been found in renal stones in association with other usual calculus components. Rare incidents of acute interstitial nephritis have been reported. Impotence has been reported in a few patients on 'Dyazide', although a causal relationship has not been established.*
Supplied: 'Dyazide' is supplied as a red and white capsule, in bottles of 1000 capsules; Single Unit Packages (unit-dose) of 100 (intended for institutional use only); in Patient-Pak™ unit-of-use bottles of 100.

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Outbreak of Hepatitis A on an Offshore Petroleum Platform, Alaska

TOM KOSATSKY, MD, MPH, *Atlanta;* JOHN P. MIDDAUGH, MD; *and* DAVID HALL, PhD, *Anchorage, Alaska*

An outbreak of 8 cases of hepatitis A among the 36-member crew of an offshore Alaska petroleum production platform was linked to a previous outbreak in an urban day-care center. Transmission of hepatitis A on the platform related most plausibly to refrigerated food items contaminated by a cook with mild disease. Control efforts included identifying and treating contacts of case patients who had traveled far from the platform before becoming ill. Early serologic confirmation of diagnosed cases and rapid reporting to public health authorities are essential to prevent disease transmission. Timely investigation can limit the administration of immune globulin to persons at high risk of contracting the disease.

(Kosatsky T, Middaugh JP, Hall D: Outbreak of hepatitis A on an offshore petroleum platform, Alaska. West J Med 1988 Feb; 148:163-166)

In a mobile society, infectious disease crosses occupational, social, and geographic boundaries. That relationships exist between the illnesses of individual patients easily goes unnoticed. The biologic characteristics of certain infectious agents can also obscure patterns of transmission. In the case of hepatitis A, a long incubation period of two to six weeks and the sometimes minor degree of illness in those infected may mask person-to-person transmission and thereby delay the institution of control measures. We report a series of cases in which early notification by physicians and comprehensive public health investigation showed the breadth of what at first appeared to be an isolated outbreak of hepatitis A.

Patients and Methods

On August 8, 1983, acute hepatitis A was identified 10 to 16 days after the onset of symptoms in three persons who had worked on a petroleum production platform in Cook Inlet, off south-central Alaska. The company operating the platform asked the State Epidemiology Office (Division of Public Health, Department of Health and Social Services, State of Alaska) to investigate and to initiate measures to control the apparent outbreak.

The platform was one of several in the Cook Inlet field. Workers on the platform (men and women) included the employees of the petroleum company and its subcontractors. Those working for the petroleum company alternated one week on the platform with one week leave on shore. Subcontractors supplied specialized services to this and its sister platforms such as catering, mud sampling, and equipment maintenance and repair. While some of these subcontractors' employees remained on the platform for as long as 14 days, most spent only several hours on board. About 12 persons were on board during any single day. Employees entered and left by helicopter and recorded their arrival and departure in a log book maintained in the helicopter bay. Meals, eaten in a large common dining area, were prepared by a resident cook. There were bedroom facilities on two levels with restrooms nearby. Unchlorinated water was pumped on board weekly. While water was not treated on the platform, samples tested routinely for coliform bacteria were said to have been consistently negative during 1983. The platform had an on-board sewage treatment plant; processed effluent drained into the ocean. Platform workers resided in the Kenai, Alaska, area near the base of operation of the platform as well as throughout Alaska and the rest of the country. Other than three cases of acute viral hepatitis that were reported August 8, no cases of hepatitis A had been reported from the Kenai area after March 1983.

We defined a case of platform-related hepatitis A as that occurring in a person on the platform during June or July 1983 who was found to have hepatitis A immunoglobulin M (IgM anti-hepatitis A virus [HAV]), the acute-phase antibody. Serum specimens were obtained in mid-August from all 36 platform workers whose presence on the platform between June 27 and July 8—considered to be the most likely dates of exposure to the hepatitis A virus for the three workers whose onsets of illness were in late July—was established by sign-in records. Serum was tested for IgM anti-HAV and for nonspecific hepatitis A antibody (anti-HAV), a marker of immunity to hepatitis A, by the Northern Regional Laboratory, Alaska Division of Public Health. A questionnaire was administered face-to-face to the 36 platform workers in mid-August. Responses were compared between persons with platform-related hepatitis A and workers who remained susceptible (anti-HAV- and IgM anti-HAV-negative). Questions included the frequency of consuming cold foods and drinks considered to be possible agents for transmitting the hepatitis A virus. Statistical tests of significance included the Fisher's exact and the Wilcoxon rank sum tests.

Links to cases identified by our investigation were sought with other persons whose hepatitis A had been reported to the Alaska Division of Public Health. Platform sanitation was

From the Epidemiology Program Office, Division of Field Services, Centers for Disease Control, Atlanta (Dr Kosatsky); the Epidemiology Office, Division of Public Health, Alaska Department of Health and Social Services (Dr Middaugh), and the Alaska Investigations Division, Center for Infectious Disease, Centers for Disease Control, Anchorage (Dr Hall). Dr Kosatsky is now at the Bureau régional en santé environnementale, Montréal, Québec.

Reprint requests to Epidemiology Program Office, Division of Field Services, Centers for Disease Control, 1600 Clitton Rd NE, Atlanta, GA 30329.

ABBREVIATIONS USED IN TEXT

HAV = hepatitis A virus
IgM = immunoglobulin M

evaluated by the Department of Environmental Conservation, State of Alaska. Water samples taken from the main tank and from all seven faucets on the platform were cultured for coliform bacteria.

Results

Of the 36 platform workers tested, 6 had hepatitis A antibody (anti-HAV), but not of the immunoglobulin M class, indicating their long-term immunity to hepatitis A. In 26 workers, tests were negative for both IgM anti-HAV and anti-HAV, indicating the workers' continuing susceptibility to infection with hepatitis A. Eight platform workers were identified whose serum was positive for IgM anti-HAV. Among them were the three persons whose cases of acute hepatitis A had been reported to the Epidemiology Office: a female cook whose illness was reported by her physician, and two employees of the petroleum company whose illness was reported by their employer. Serologic testing also identified two subcontractors' employees who had been ill with icteric hepatitis and two workers with malaise and vomiting without jaundice. The eighth person identified as having a case of platform-related hepatitis A was a male cook who had mild nausea without vomiting, diarrhea, or jaundice July 2 and 3, about three weeks before the onset of disease in seven of his coworkers. An earlier investigation by the Epidemiology Office had identified this cook's wife as having serologically confirmed hepatitis A with onset May 26, following illness in a child at the day-care center that she managed. The husband/cook did not receive immune globulin prophylaxis following his wife's illness. Dates of the onsets of illness in the eight platform workers with cases of hepatitis A and the cook's wife are shown in Figure 1.

While a plausible source of infection external to the platform could be found for the male cook, the seven workers who became ill July 19 through 26 had no evident external source. None were aware of contact with family or friends with hepatitis A. All said they had had no recent exposure to situations known to be related to acquiring hepatitis A, particularly homosexuality, day-care centers, consumption of raw shellfish, and travel to third world countries.

Sign-in records were used to plot the presence on the platform, day by day, of the 22 susceptible (IgM anti-HAV- and anti-HAV-negative) workers and their 8 ill colleagues. The days that each infected person (designated 1 through 7, and male cook) and each susceptible person (not numbered) were present on the platform are shown in Figure 2. Also shown are the days during which the cook claimed to feel ill. Two distinct periods appear to be associated with transmission: days up to July 1 for platform-related cases 2 through 6 (Figure 2) and July 4 and the days following for cases 1 and 7 (and possibly 3 and 6). By July 4 to 5, when workers who became cases 1 and 7 entered the platform, the cook was no longer present.

We compared demographic characteristics and questionnaire responses for the 7 workers who became ill with hepatitis A July 19 through 26 and the 22 who remained susceptible. The infected group included one woman and six men. Their ages ranged from 21 to 46 years (median 38 years). The noninfected, susceptible group included 1 woman and 21 men. Their ages ranged from 20 to 53 years (median 29 years). During the interval June 27 through July 8, all members of the infected group spent at least one night on the platform (median four nights). Among the 22 noninfected workers were 8 who spent no nights (and a median of several hours) onboard and 14 who slept on the platform (median, four nights). No appreciable differences were found between the infected and noninfected groups with respect to which restrooms or which bedrooms (comparing those who slept on board) they used on the platform.

We compared the food preferences of infected and susceptible noninfected workers. Responses (Table 1) were analyzed, including and excluding the eight workers whose presence on the platform had been confined to one or two daytime

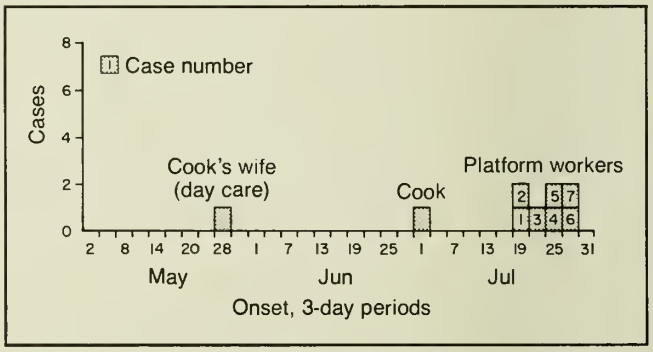

Figure 1.—The graph shows cases of hepatitis A, by dates of onset, on an offshore platform, Alaska, May 2 through July 31, 1983.

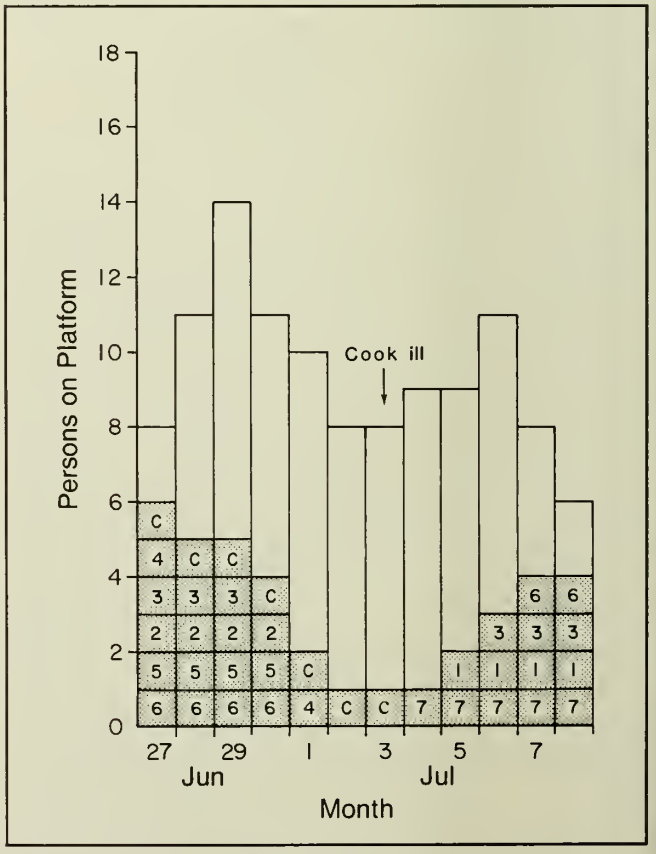

Figure 2.—The graph shows persons present on the offshore petroleum platform, Alaska, June 27 through July 8, 1983. □ = susceptible, noninfected person, [C] = infected cook, [1] = infected person, by case number

TABLE 1.—*Evaluation of Selected Food Items as Possible Risk Factors for Hepatitis A Infection of Susceptible Persons on the Offshore Platform, Alaska, June 27-July 8, 1983**

Item (Number of Workers)	Question: On the platform, do you eat Regularly	Sometimes	Rarely	Never	Z†	P (2-sided)
Ice						
Infected (7)	7	0	0	0	.	.
Noninfected (22)	9	6	3	4	−2.319 ‡	0.0204
Noninfected, day workers excluded (14)	8	5	0	1	−1.567 ‡	0.1172
Iced tea						
Infected (7)	2	1	1	3	. .	.
Noninfected (22)	8	3	5	6	0.5606	0.5751
Noninfected, day workers excluded (14)	7	3	2	2	1.2310	0.2183
Water						
Infected (7)	4	1	1	1	. . .	. . .
Noninfected (22)	10	5	4	3	−0.3568	0.7213
Noninfected, day workers excluded (14)	6	4	3	1	−0.2984	0.7654
Potato salad						
Infected (7)	3	1	2	1	. . .	. . .
Noninfected (22)	2	5	2	13	−1.9367	0.0528
Noninfected, day workers excluded (14)	2	3	2	7	−1.4921	0.1357
Fruit salad						
Infected (7)	3	2	1	1	. . .	. . .
Noninfected (22)	2	1	7	12	−2.3699	0.0178
Noninfected, day workers excluded (14)	1	0	6	7	−2.3127	0.0207

*Excludes the cook, who had onset of his illness July 2-3.
†Wilcoxon rank sum test.
‡Comparisons were made between infected (7 workers) and noninfected (22) and between infected (7) and noninfected workers who spent at least one night on the platform (14).

visits. No relationship was shown between the frequency of consuming water (or water-based iced tea and fruit-mix drink) and illness. A variety of salads was available on the platform; we questioned workers about eating the green salad, potato salad, and fruit salad. Fruit salad was most strongly associated with illness, and this effect remained when only workers who slept on board—that is, spent more time, and were likely to have eaten more meals—were included. Ice showed a relationship to illness that became weaker when only workers who slept on board were included.

Inspection of the platform by trained sanitarians showed that the platform sewage discharge line was located close to an uncapped water intake; back-flow control devices were absent in the water system hose; potential cross-connections existed between potable water lines and tanks for the storage of water used in sea bed drilling; water on board the platform was not disinfected at its source before its use; cold salads were prepared by the cook and were held chilled for several days; the ice machine had a chest for the storage of cubes and automatically refilled when the weight of ice fell below a threshold level. Cultures of potable water taken from all areas of the platform were negative for coliforms.

Control Measures

Immune Globulin Prophylaxis

In all, 39 persons present on the platform July 20 through 28 in whom hepatitis A did not develop were treated with immune globulin. Private physicians and public health authorities also administered immune globulin to at least 54 family members and others who had shared accommodations with the five workers in whom icteric hepatitis A developed. Four of the five had left the Kenai, Alaska, area before becoming ill; immune globulin was administered to contacts as far away as Idaho and Ontario, Canada. The serologic diagnosis of anicteric hepatitis A was made for three workers (including the male cook) more than three weeks after the onset of their illness; immune globulin was not offered to their household contacts. An active search revealed no cases of platform-related hepatitis A occurring after July 27, 1983.

Platform Hygiene

Recommendations for improving hygienic practices were made to the petroleum company by the Alaska Departments of Health and Social Services and Environmental Conservation. In accordance with these recommendations, the platform's sewage discharge line was moved to a location where sewage spray could not contact the water supply hose. Cross-connections were eliminated on the platform's water systems; back-flow protection devices were installed between the kitchen and the restrooms. Potable water on the platform is now iodinated (although chlorination was recommended). Loads of potable water pumped on board the platform are now analyzed for coliforms on a monthly basis. Salads are not kept longer than two days.

Discussion

While their mobility after leaving the platform necessitated a control program of international scope, that platform workers were exposed to hepatitis A virus in such a confined and controlled setting allowed for a thorough study of the circumstances of their infection. Sign-in records allowed us to focus our investigation on 36 workers. As in a food handler-related outbreak reported by Snydman and associates,[1] retrospective serology helped identify the likely source of infection and showed who among the exposed workers was immune, who was susceptible, and who had been recently infected. The anti-HAV test established that six platform workers were immune to infection, and the IgM anti-HAV test confirmed five cases with icterus and established three cases in which jaundice did not develop. One of the patients, a

platform cook, was linked to an earlier outbreak of hepatitis A in a day-care center managed by his wife.

This outbreak of hepatitis A reflects the contemporary epidemiology of the disease.[2] Of 36 platform workers tested, 30 (83%) were susceptible to infection in July 1983. Such low levels of immunity have been commonly found in North Americans 20 to 40 years of age.[3] The likely connection of this outbreak to infant day care reflects the increasing role of these centers in the transmission of enteric viruses between diapered children and parents and adult care givers.[4]

It appears likely that platform workers were infected with hepatitis A virus over the course of several days. Indeed, if all infections were transmitted on the platform, hepatitis A virus must have been viable for the minimum period of June 29 through July 5 to have infected all seven persons who subsequently became ill. It has been shown in studies done in both humans and animals that hepatitis A virus is typically shed over a period of several days, with maximal shedding (and infectivity) just preceding the onset of symptoms.[5] Possibly the cook shed hepatitis A virus over several days during his shift. The infection of at least two workers who entered the platform only after the cook's departure must be explained by the persistence of virus in one or more vehicles.

Because it was six weeks after the time of exposure to the hepatitis A virus when platform workers were interviewed, we relied on reported food preference rather than the recall of specific foods eaten to indicate the most likely vehicles of the transmission of hepatitis A. Of the foods we studied, contaminated fruit salad followed by contaminated ice was most consistent with the food preferences of ill as compared with well platform workers. Survival of hepatitis A virus has been documented in refrigerated foods for a period of days.[2] Ice, if contaminated in the freezer by the cook just before the onset of his illness, would certainly have kept the hepatitis A virus viable, as would a refrigerated fruit salad that was re-served for several days. Although sanitary inspection indicated sewage disposal as a possible route for contaminating platform water, epidemiologically there was no evidence that frequent consumers of water or water-based drinks were any more likely to have contracted hepatitis A than infrequent consumers. Other than our observation that salads were held chilled for extended periods, the roles of food preparation and of the cook's hygiene were not evaluated.

Early notification and prompt investigation of this outbreak allowed for a timely assessment of who was at risk for contracting hepatitis A. Investigation established that all cases were associated with one of the many platforms in the petroleum production field. Seven hepatitis A patients were identified whose onsets of illness occurred in a cluster during July 19 through 27. Because one member of this group was also a cook and considering the close living quarters on the platform, we decided to administer immune globulin to workers who had been in contact with their seven ill associates during the time that the seven would most likely have been shedding hepatitis A virus. Our ability to target a group at high risk prevented the much broader administration of immune globulin to workers on other platforms and to those working on this platform at other times.

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Perfusion Lung Scans Provide a Guide to Which Patients With Apparent Primary Pulmonary Hypertension Merit Angiography

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There is hesitancy, based on the perceived risk, to do pulmonary angiography in patients believed to have primary pulmonary hypertension. Yet pulmonary hypertension due to major-vessel, chronic thromboembolism mimics primary pulmonary hypertension clinically and on standard laboratory tests. Because thromboembolic pulmonary hypertension is potentially remediable by thromboendarterectomy and primary pulmonary hypertension is not, differentiating between these disorders is essential. Angiography is required in patients with thromboembolic pulmonary hypertension to define the anatomic location of the thrombi. In evaluating perfusion lung scans of 110 patients with pulmonary hypertension to determine whether the scan might provide a guide to selecting those patients who merit angiography, no segmental-size perfusion defects were noted on the scans of 64 patients with primary pulmonary hypertension, whereas all 46 patients with thromboembolic hypertension had one or more defects that were segmental in size or larger. These data indicate that a perfusion lung scan should be done in patients with pulmonary hypertension of uncertain cause and that those with one or more segmental or larger defects merit pulmonary angiography before being diagnosed as having primary pulmonary hypertension.

(Moser KM, Page GT, Ashburn WL, et al: Perfusion lung scans provide a guide to which patients with apparent primary pulmonary hypertension merit angiography. West J Med 1988 Feb; 148:167-170)

Primary pulmonary hypertension remains enigmatic in pathogenesis, is nominally responsive to therapy, and has a poor prognosis.[1-4] On the other hand, pulmonary hypertension due to chronic thromboembolic obstruction of major (main, lobar, segmental) pulmonary arteries is of a known cause and is potentially correctable by thromboendarterectomy.[5-9] Therefore, differentiating between these two disorders is essential, but it may be difficult. The history, physical examination, and standard laboratory tests—chest x-ray films, electrocardiogram (ECG)—and right heart catheterization may provide no differential clues.[5,9,10] Indeed, only the results of pulmonary angiography can unequivocally make the diagnosis. Yet, there is reluctance to do angiography in all patients with apparent primary pulmonary hypertension because of the perceived risk.[1,11,12]

Limited prior experience at our institution and others has suggested that the perfusion lung scan might assist in the decision to do pulmonary angiography in patients with severe, unexplained pulmonary hypertension.[13-15] To determine whether this suggestion could be validated in a large series, we have reviewed perfusion lung scans and collateral data in 110 patients: 64 who had primary pulmonary hypertension and 46 who had pulmonary hypertension due to major-vessel thromboembolism. The data confirm that the perfusion scan provides a highly reliable guide to selecting patients who merit pulmonary angiography.

Patients and Methods

The 64 patients with primary pulmonary hypertension were referred to various centers, including the University of California, San Diego (UCSD), that are participating in the National Heart, Lung, and Blood Institute's Primary Pulmonary Hypertension Registry; after evaluation, the patients met the criteria for registry inclusion.[16] The entry criteria include compatible findings on a history, physical examination, and chest radiograph; a right heart catheterization confirming pulmonary hypertension in the absence of a left-to-right cardiac shunt, or an elevated pulmonary capillary ("wedge") pressure; and pulmonary spirometric tests excluding significant restrictive or obstructive abnormalities. While pulmonary angiography or a lung biopsy are not required for entry in the registry, 57 (89%) of these 64 patients did have pulmonary angiographic (44 patients), lung biopsy (6 patients), or autopsy (7 patients) confirmation of the diagnosis of primary pulmonary hypertension. This is a substantially higher rate of angiographic-biopsy-autopsy confirmation than exists among the approximately 300 patients admitted to the registry thus far.

The 46 patients with chronic thromboembolic pulmonary hypertension were all evaluated at the UCSD Medical Center, and 38 of them ultimately underwent thromboendarterectomy between 1970 and 1985. All were referred for evaluation of pulmonary hypertension of an uncertain cause. All

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ABBREVIATIONS USED IN TEXT

ECG = electrocardiogram
UCSD = University of California, San Diego

had pulmonary angiography. (Angiography also disclosed that 16 patients referred during this period had primary pulmonary hypertension, and these are included in the series of registry patients.)

All 110 patients had perfusion scans, including at least four views (anterior, posterior, and both laterals). Most (92 patients) also had either ventilation scans using xenon Xe 133 or inhalation scans using technetium Tc 99m-labeled pentetic acid (sodium zinc diethylenetriaminepentaacetate, DTPA). The scans from all patients, with all identifiers removed, were intermixed in a random fashion and submitted to two reviewers experienced in interpreting scans. They were asked, first, to classify the perfusion scans into two categories: those with one or more segmental or larger defects and those without defects of this size. They were also asked to subclassify those in the second category as to whether the distribution of radioactivity was inhomogeneous—specifically, to classify those with no or equivocal inhomogeneity as normal and those with unequivocal differences in regional radioactivity as inhomogeneous. Finally, the reviewers were asked to note the presence of any subsegmental defects or defects due to cardiac or other vascular structures.

Results

Analysis of the scan classification according to the presence or absence of segmental or larger defects disclosed no disagreement between the two reviewers. Furthermore, none of the 64 patients with primary pulmonary hypertension had such defects, whereas all 46 patients with pulmonary hypertension due to chronic, major-vessel thromboembolism had one or more defects that involved one or more segments. Thus, there was no overlap in classification between the two groups.

Among the 46 patients with thromboembolic pulmonary hypertension, all ventilation scans were classified as normal—that is, these defects showed a ventilation-perfusion "mismatch" (Figure 1).

The reviewers also agreed on the subclassification among 60 of the 64 patients without segmental defects. Of the 60 patients, 41 were classified as showing either no or minimal inhomogeneity; 6 of these also showed one subsegmental defect (Figure 2). In 19, the reviewers agreed that the distribution was inhomogeneous (Figure 3); of these, 2 also had subsegmental defects. In four patients, there was disagreement as to whether more than minimal inhomogeneity was present.

Two other types of abnormalities were seen in some patients with both forms of pulmonary hypertension. One type was due to the pronounced cardiomegaly present in some patients (Figures 4 and 5). On the anterior scan view, cardiomegaly widened the "cardiac space" normally seen and encroached on the left lower lobe. On the posterior view, it diminished scan perfusion to the left lower lobe, and, often, on one or both lateral views, cardiomegaly was reflected as diminished to absent perfusion to the lower anterior lung zones.

The second common scan abnormality was due to increased size of the central pulmonary arteries (Figures 2, 4, and 5). Decreases in perfusion to areas corresponding to these arteries were often seen in anterior, posterior, and lateral views.

Discussion

The pathogenesis of "primary" pulmonary hypertension is uncertain. The World Health Organization has recom-

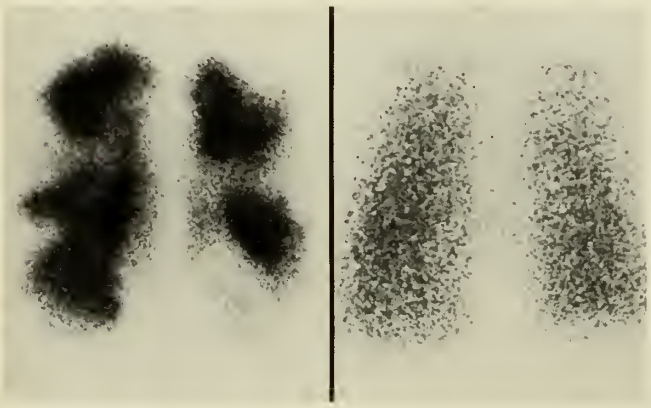

Figure 1.—Left, A perfusion scan is shown of a patient with pulmonary hypertension due to chronic obstructing thromboembolism who subsequently underwent thromboendarterectomy. Many segmental defects are present in both lungs. **Right,** The ventilation scan was normal during wash-in of xenon Xe 133 (shown) and during wash-out.

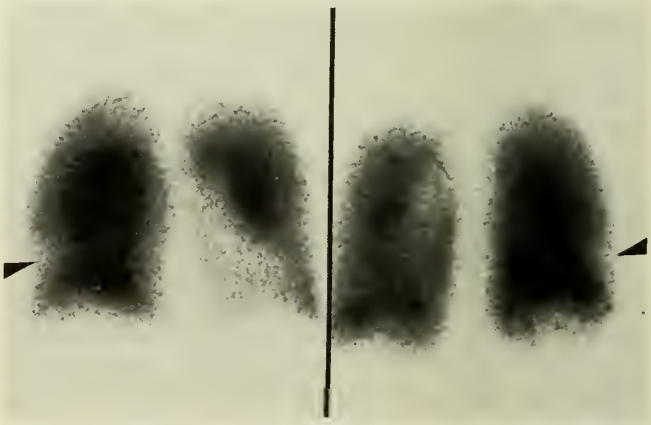

Figure 2.—Perfusion scans are normal in a patient with primary pulmonary hypertension except for a subsegmental defect **(arrow)** on anterior **(left)** and posterior **(right)** views. A left pulmonary artery imprint is seen on the posterior view. The patient's pulmonary angiogram disclosed no embolic obstruction.

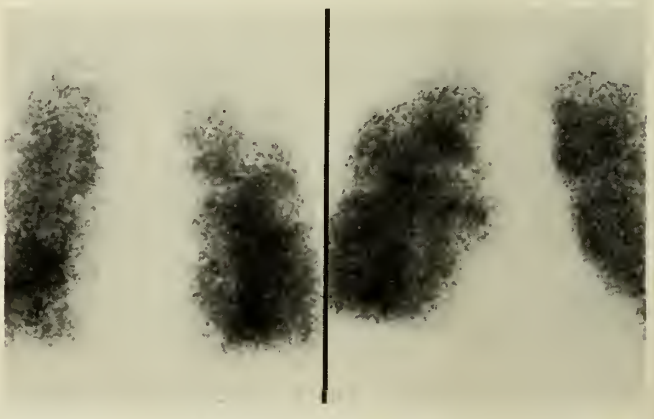

Figure 3.—A perfusion scan in a patient with primary pulmonary hypertension shows an inhomogeneous distribution of radioactivity on anterior **(left)** and posterior **(right)** views.

mended separating primary pulmonary hypertension into three categories on the basis of histologic findings, namely, plexogenic pulmonary arteriopathy, microthrombotic pulmonary hypertension, and pulmonary veno-occlusive disease.[17] Whether these three conditions are pathogenetically distinct remains uncertain. There is a fourth disorder, however—chronic, major-vessel thrombotic pulmonary hypertension—that differs from those comprising "primary" pulmonary hypertension in important ways. Indeed, it might be clarifying to describe primary pulmonary hypertension as

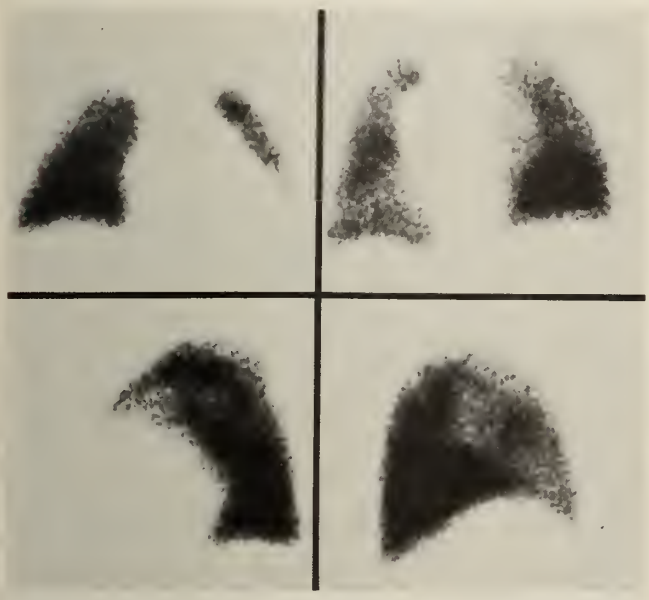

Figure 4.—A perfusion scan done in a patient with primary pulmonary hypertension and marked cardiomegaly shows substantial widening of the cardiac space, with particular encroachment on the left lower lobe in anterior **(upper left)** and posterior **(upper right)** views. The left lateral view **(lower left)** shows a large anterior cardiac imprint. Pulmonary artery imprints are seen well on posterior and right lateral **(lower right)** views.

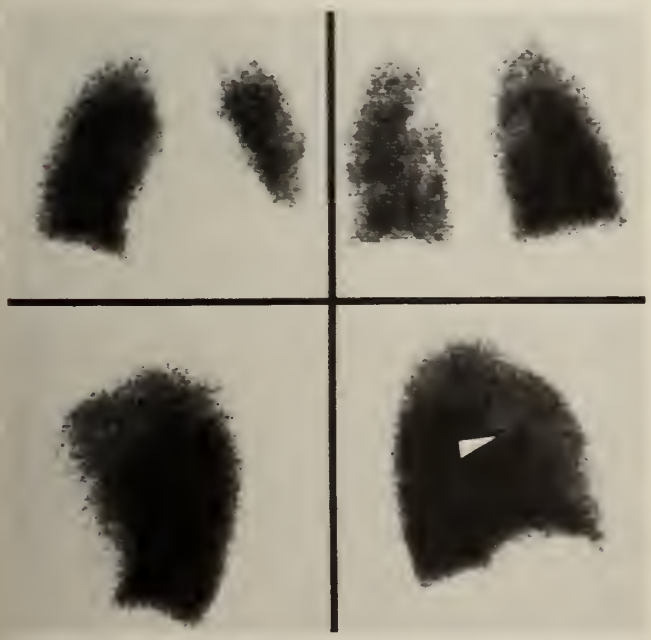

Figure 5.—Left and right pulmonary arteries in a patient with primary pulmonary hypertension cause imprints on the posterior view **(upper right)** and the right lateral view **(lower right, arrow)**. Cardiomegaly also is present.

"small-vessel obliterative pulmonary hypertension" to distinguish it from the major-vessel form in which the obstruction involves main, lobar, and segmental pulmonary arteries. The distinction is more than anatomic; it conditions therapeutic options. Small-vessel obliterative pulmonary hypertension is not subject to correction by surgical thromboendarterectomy, whereas the disorder due to major-vessel thromboembolism is.[5-10]

Despite the importance of this differential diagnosis, we and others have found that many patients with thromboembolic pulmonary hypertension have been labeled, for varying periods of time, as having primary pulmonary hypertension.[5-10] This is understandable because the two conditions closely mimic each other with regard to clinical findings and the results of standard laboratory tests, such as ECG, chest radiography, pulmonary function, and right heart catheterization findings.[9,10] Yet, the diagnostic delay in making this distinction may be unfortunate for several reasons. First, the patients with thromboembolic pulmonary hypertension have been told of the rather grim prognostic outlook for the primary form. Second, and more important, misdiagnosis as primary pulmonary hypertension often has delayed the consideration of a thromboendarterectomy for months to years. This delay has, in a number of instances, led to a deterioration in right ventricular function and a patient's overall status, factors that increase the risk of surgical thromboendarterectomy.[9,10] Furthermore, there is evidence that a delay in doing a thromboendarterectomy may be associated with progressive injury to the pulmonary arterial vessels,[5,18] a development that also may increase the surgical risk and may moderate and delay post-operative pulmonary hemodynamic improvement.[9,10]

Often the diagnostic delay has been based on a reluctance to do pulmonary angiography in patients diagnosed as having primary pulmonary hypertension because of prior reports that this procedure entails substantial risk.[11,12] While more recent reports indicate that modern methods for angiography pose substantially less risk in patients with pulmonary hypertension,[19,20] it would be useful if a safe, noninvasive technique were available to guide selection of those who merit angiography.

Previous reports of small series of patients have suggested that perfusion lung scanning might fill this role.[13-15] The present report of a large series confirms the reliability of the perfusion scan in differentiating primary pulmonary hypertension from potentially operable thromboembolic pulmonary hypertension. Using the simple criterion of the presence or absence of one (or more) perfusion defects that are the size of a lung segment or greater, there was no overlap between patients with the primary type and those with the thromboembolic type of hypertension. In the 46 patients in whom perfusion defects were found involving one or more segments, pulmonary angiography confirmed chronic thrombotic occlusion of one or more lobar or segmental arteries. We would suggest, therefore, that before a patient is characterized as having primary pulmonary hypertension on the basis of clinical and laboratory studies—including right heart catheterization—lung scanning should be done. If this procedure discloses one or more segmental or larger "mismatched" perfusion defects, pulmonary angiography is warranted.

The question could be raised as to the need for angiography even among patients with thromboembolic pulmonary hypertension, if the scan is so definitive. The answer lies in the

fact that locating the thrombi precisely is an essential antecedent to surgical treatment.[10] In patients with thrombi limited to segmental or subsegmental arteries, a thromboendarterectomy may be difficult or impossible to do.[5,9] A lung scan cannot distinguish whether segmental or larger defects are due to one proximal obstruction or several more distal obstructions. Only angiography can provide such anatomic information. The decision for thromboendarterectomy is, of course, not based exclusively on detecting scan or angiographic abnormalities, as we have described elsewhere.[10] For example, we require a pulmonary vascular resistance above 300 dynes·sec·cm^{-5} before surgical treatment is recommended.

It is also reasonable to consider whether the excellent perfusion scan separation between primary pulmonary hypertension and major-vessel thromboembolic hypertension may, in part, reflect some bias in patient selection in the present series. For example, it is theoretically possible that there are patients with major-vessel thromboembolic pulmonary hypertension in whom segmental or larger mismatched defects may be absent. This would require critical placement of partially obstructing thrombi—for example, in both main pulmonary arteries. While we have seen such an occurrence in animals, this has not yet been reported in humans.

On the other hand, may there not be patients with primary pulmonary hypertension in whom the scan will show segmental or larger defects? In our own experience, in which all patients with pulmonary hypertension of an uncertain cause have undergone angiography, this has not yet occurred. Nor are we aware of a patient studied elsewhere in whom such a scan-angiographic disparity has occurred. Thrombosis does occur in the *distal* pulmonary arteries in some patients with primary pulmonary hypertension.[13] In a recent report, this was suggested as the basis for the inhomogeneous lung scan pattern, whereas a homogeneous pattern may reflect plexogenic pulmonary arteriopathy[21]; but no segmental-sized defects have been reported in such patients.

In summary, the extensive experience reported here indicates that perfusion lung scanning provides an excellent noninvasive low-risk tool for distinguishing between pulmonary hypertension due to potentially operable large-vessel chronic thromboembolism and obliterative, small-vessel pulmonary hypertension ("primary"). This experience suggests that patients with one or more segmental or larger perfusion defects who are considered candidates for correction by surgical thromboendarterectomy should undergo arteriography. Continued study of scan-angiographic relationships is warranted to determine whether exceptions to the findings reported here may occur.

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Heterosexual and Perinatal Transmission of Human Immunodeficiency Virus in a Low Prevalence Community

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Six previously unidentified cases of human immunodeficiency virus (HIV) infection were found during an investigation and follow-up of three clusters of heterosexually and perinatally transmitted HIV infections. The investigations were to identify those infected, to interrupt the transmission of HIV, to attempt to reduce the likelihood of the development of the acquired immunodeficiency syndrome among those found to be seropositive, and to show the usefulness of traditional disease control strategies during this epidemic. Our findings indicate the value of contact tracing for HIV infections and the need to provide and evaluate educational activities regarding the transmission of HIV in low prevalence populations.

(Taylor AF, Johnson S, Wyant SR, et al: Heterosexual and perinatal transmission of human immunodeficiency virus in a low prevalence community. West J Med 1988 Feb; 148:171-175)

The epidemiology of the acquired immunodeficiency syndrome (AIDS) in California differs from that in the United States in that sexual contact between men explains 93% of the California cases compared with 72% of cases nationwide.[1,2] Intravenous drug use in California (exclusive of male sexual contact) explains only 2% of the cases while being associated with 17% of the national cases. Heterosexual transmission has been associated with about 2% of cases nationwide and less than 1% of the California cases. In San Bernardino County, 5% of the reported cases have been attributed to heterosexual contact. Several authorities believe heterosexual transmission of the human immunodeficiency virus (HIV) will become increasingly important in the epidemiology of AIDS.[3-7] The Centers for Disease Control (CDC) have projected that 5% of the national cases will be associated with heterosexual contact by 1991.[8] We believe the need exists to identify heterosexuals who are infected with HIV. Education after identification appears to be a reasonable method to interrupt further transmission.[9-15]

Concern in the gay community about violation of confidentiality and the resultant discrimination led to legislation—California Health and Safety Code §199.21 *et seq*—that has hampered contact tracing efforts in California. It is illegal for anyone to disclose a patient's HIV antibody status without specific written consent if the person does not meet the CDC criteria for AIDS. However, we feel that these concerns should not limit efforts to prevent the transmission of the infection in the community at large (J. Chin, MD, "Rapid Investigation of Selected AIDS Cases," and "Contact Tracing of Partners of HTLV-III Antibody Positive Men," letters to California AIDS surveillance/epidemiology personnel, February 13, 1985, and August 14, 1985, respectively).

Herein we describe the disease-control activities involved in investigating three clusters of heterosexually transmitted HIV infections and resultant perinatal infections. These investigations spanned three states and four California counties.

Persons and Methods

We used traditional communicable disease interviewing and contact tracing. In California, cases of AIDS that satisfy the CDC surveillance definition are reportable by law (Cal Admin Code title 17, §2503). All reports are investigated using the CDC standard report form by trained, experienced public health investigators. The county also participates in legally mandated HIV antibody testing that is anonymous and free, the stated purpose of which is to protect the donated blood supply. In both instances, evidence of risk behaviors for HIV infection is elicited. These interviews and subsequent investigations were prompted by reports of AIDS or HIV infection where heterosexual transmission was suspected—that is, where no other identifiable risk could be elicited. The subjects were asked to identify all their sex partners in the previous seven years. This period was used because it roughly corresponds to the introduction of HIV into the United States. Any sex partner identified as being positive for the HIV antibody was similarly interviewed for contacts. Children of women with serologic evidence of infection were tested. Contacts found to be seronegative received no follow-up other than education about preventing HIV transmission.

All patients were advised before testing that, should their tests be positive, they would be referred to a physician knowledgeable about HIV infections and for psychological counseling, if requested.

Written informed consent was obtained before collecting blood specimens. Enzyme immunoassay tests were supplemented with an indirect immunofluorescence assay when the initial tests were positive.

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ABBREVIATIONS USED IN TEXT

AIDS = acquired immunodeficiency syndrome
ARC = AIDS-related complex
CDC = Centers for Disease Control
HIV = human immunodeficiency virus
IV = intravenous

Results

To protect the identity of all persons involved, ages are presented in deciles, with the exception of the pediatric cases, which are presented in standard epidemiologic age groups.

Cluster One

In 1985, the San Bernardino County Department of Public Health received its first report of a case of AIDS whose probable source was heterosexual contact. The patient, a woman in her 30s, was diagnosed with *Pneumocystis carinii* pneumonia and esophageal candidiasis. When interviewed, she identified two of her sex partners over the past seven years as intravenous (IV)-drug-using men, one a bisexual.

A description of the investigation follows (see Figure 1).

Person A. This woman in her 30s was positive for the HIV antibody and had AIDS. The patient said she did not use drugs intravenously and had no history of transfusion. She did report having sex partners (persons E and G) who engaged in high-risk behaviors. The patient subsequently died, with AIDS as the primary cause of death.

Person B. The daughter of the index case is younger than 1 year. The child was tested and found to be positive for HIV antibodies. She has the wasting syndrome and recurrent bacterial respiratory infections.

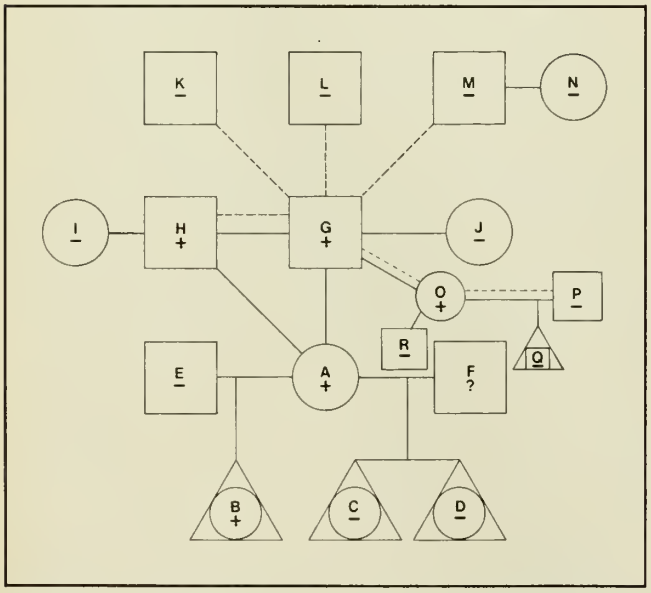

Figure 1.—The diagram shows heterosexual, perinatal, and possibly parenteral transmission of the human immunodeficiency virus (HIV). HIV seropositivity is indicated by a plus sign. Female A had no risk factors other than heterosexual contact with males G and H during the latter half of 1983. Males G and H were both identified as bisexual and intravenous (IV)-drug users. Heterosexual transmission may have also occurred between male G and female O during the spring of 1984. These persons also shared needles, however, so parenteral transmission cannot be ruled out. Perinatal transmission was the probable source of infant B's infection, as no other risk factors could be identified. □ = male, ○ = female, △ = child, --- = IV drug exposure

Person C. A daughter of the index case in the 5- to 9-year age group was negative for the antibody to HIV.

Person D. A daughter of the index case in the 10- to 14-year age group was negative for the antibody to HIV.

Person E. A man in his 20s and the father of B was determined to be negative for the HIV antibody despite a history of IV-drug use. His period of sexual exposure to A was late 1983 through the spring of 1985.

Person F. The father of C and D was never located. He was not known to be an IV-drug user or sexually active with men. The period of exposure to A could not be elicited.

Person G. This incarcerated bisexual man in his 20s had a history of IV-drug use. He was positive for the HIV antibody, subsequently *P carinii* pneumonia developed, he was classified as having AIDS, and died. Prison officials reported him to be an IV-drug contact of M (below). According to A, her period of sexual contact with G was the latter half of 1983.

Person H. This bisexual man in his 20s had a history of IV-drug use. He was positive for the HIV antibody and diagnosed to have cryptococcal meningitis and *P carinii* pneumonia. He has since died. His period of sexual and parenteral exposure to G was late 1983. His period of sexual exposure to A was also late 1983.

Person I. This woman in her teens, a sexual partner of H, was found to be negative for the HIV antibody. Her period of sexual exposure was the fall of 1985 to mid-1986. She presented to our clinic upon the death of H. During the course of the interview she named H as a parenteral and sexual contact to G and a sex partner of A.

Person J. This woman in her 20s, a sex partner of G, was negative for the antibody to HIV. Her period of sexual exposure was 1985 to 1986.

Person K. This man in his 20s, an IV-drug contact to G, was negative for the antibody to HIV. His period of parenteral exposure was 1978 to 1984.

Person L. This bisexual man in his 20s, an IV-drug contact to G, was negative for antibody to HIV. His period of parenteral exposure could not be elicited.

Person M. This man in his 30s, who was an IV-drug contact to G while they were in prison, was found to be negative for the HIV antibody. His period of parenteral exposure to G was late 1984 to spring 1985. During the course of the interview, M named K and L as IV-drug contacts to G and J as a sex partner of G.

Person N. This woman in her 20s, a sex partner of M, was reported negative for the HIV antibody.

Person O. This pregnant woman in her 20s was classified as having AIDS in 1986 based on the diagnosis of *P carinii* pneumonia and a positive HIV antibody test. In view of her diagnosis, she terminated her pregnancy. During her interview, she admitted to IV-drug use and working as a prostitute in New York City during 1981 and Phoenix during 1985. In the interim she worked in Boston, Seattle, and a small city in Washington. She named G and P as IV-drug and sex contacts. Her period of exposure to G was the spring of 1984. She also reported observing G having sex with other men. Her period of exposure to P was mid-1984 to the fall of 1986.

Person P. This IV-drug-using man in his teens was the spouse of O and was found in another state to be negative for the HIV antibody.

Person Q. This male child of O and P in the 1- to 4-year age group was reported negative for the HIV antibody.

Person R. This man in his 20s presented to our clinic five

days after sexual exposure to O. He was negative for the HIV antibody on days 0, 30, 60, and 90.

Cluster Two

The second cluster was investigated in 1986 after a woman in her 20s was diagnosed with oral candidiasis and was positive for the HIV antibody. A description of this investigation follows (see Figure 2).

Person A. This woman in her 20s had oral candidiasis and was positive for the HIV antibody. The patient said she did not use drugs intravenously and had no history of transfusion. Her only reported sex partners were her husband (B) and a former boyfriend (C) who had hemophilia. Disease due to *Mycobacterium avium-intracellulare* later developed in this patient, and she was classified as having AIDS. She has since died.

Person B. This man in his 20s, the spouse of A, was found to be negative for the HIV antibody. He has remained negative during the course of this investigation. This man was never interviewed as he elected to be tested by his private physician.

Person C. This man in his 20s, a sex partner of A, was found to be positive for the HIV antibody. The patient indicated he was afflicted with hemophilia A. He had not been tested before our investigation but had been told by his physician that he had been treated with factor VIII concentrate from a person known to have AIDS. He has remained well during the course of this investigation. He is considered to be the probable source of A's and E's infections, and his source is in all probability factor VIII concentrate. His period of sexual exposure to A was 1979 to 1983.

Person D. This woman in her 20s, a sex partner of C, was reported negative for the HIV antibody. Her period of exposure was 1982 to 1983.

Person E. This woman in her 20s, a sex partner of B, C, F, and G, was found to be positive for the HIV antibody. During her interview she reported she had had right axillary lymphadenopathy six months previously. Her physician accurately identified her condition as "viral infection for which nothing could be done." The physician, however, did not consider HIV infection in the differential diagnosis. Other than the lymphadenopathy, the patient has remained well. Her period of sexual exposure to C was 1983 to 1985.

Person F. This man in his 20s, a sex partner of E, was found to be negative for the HIV antibody. His period of exposure to E was 1985 to 1986.

Person G. This man in his 20s, who was a sex partner of E, was not located.

Person H. This woman in her 20s, a sex partner of C, was found to be negative for the HIV antibody. Her period of exposure was 1984.

Person I. This woman in her 20s, a sex partner of C, was found to be negative for the HIV antibody. Her period of exposure was 1984.

Person J. This woman in her 20s, a sex partner of C, was reported as negative for the HIV antibody. Her period of exposure was 1985.

Person K. This woman in her 20s, a sex partner of C, was found to be negative for the HIV antibody. According to C, hers was a single exposure in 1984.

Person L. This woman in her 30s, a sex partner of C, was found to be negative for the HIV antibody. Her period of exposure was 1985 to 1986.

Cluster Three

The third cluster was investigated in 1986 after our department was asked to confirm a positive serology on a man in his 20s who had generalized lymphadenopathy. Our investigation identified the following (see Figure 3):

Person A. This man in his 20s with generalized lymphadenopathy was positive for the HIV antibody. The patient

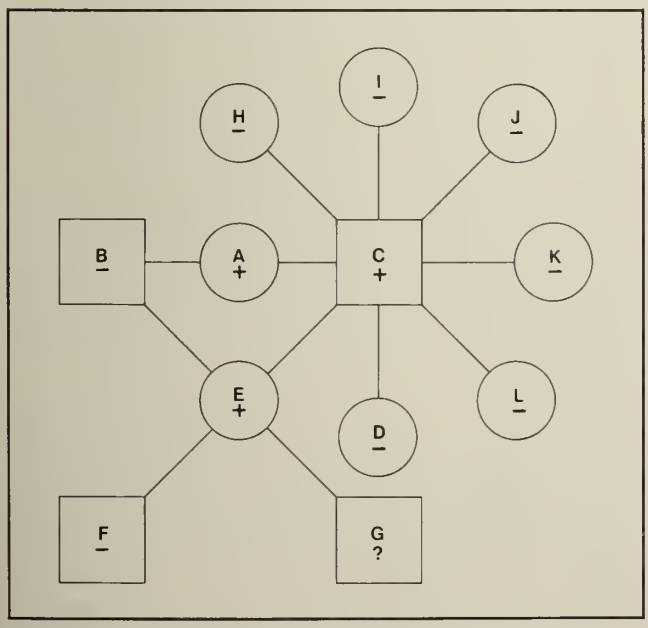

Figure 2.—The diagram shows heterosexual transmission of the human immunodeficiency virus (HIV). HIV seropositivity is indicated by a plus sign. Female A was a sex partner of male C between 1979 and 1983. Male C was identified as having hemophilia. Female E was a sexual partner of male C between 1983 and 1985. Neither of the women had any risk factors other than sexual contact with a hemophiliac. ○ = female, □ = male

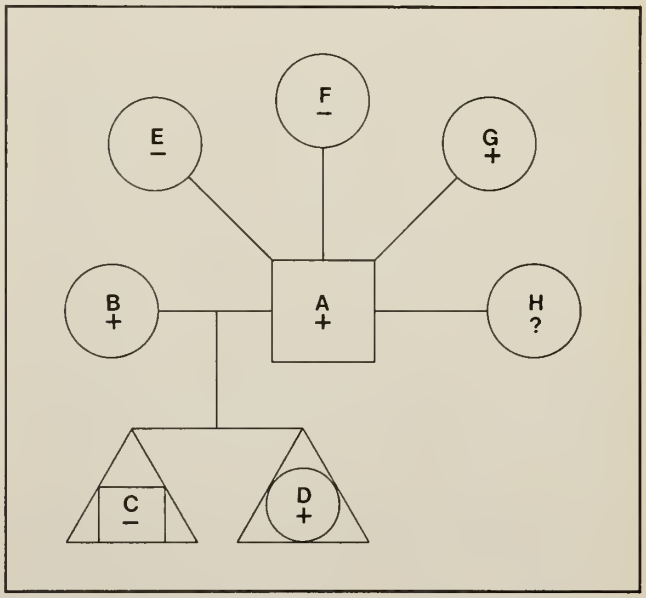

Figure 3.—The diagram shows heterosexual and perinatal transmission of the human immunodeficiency virus (HIV). HIV seropositivity is indicated by a plus sign. The investigation suggested sexual transmission from female G to male A. No other risk factors could be identified for male A. Female B had no risk factors other than sexual contact with male A. Perinatal transmission was the probable source of infant D's infection, as no other risk factors could be identified. ○ = female, □ = male, △ = child

said he did not use IV drugs or have sex with men. He did, however, report a former female sex partner (G) as having "swollen glands, just like mine." He named four additional sex partners during the study period. The patient was recently admitted to hospital with unremitting diarrhea, but he had not been diagnosed with a condition meeting the CDC surveillance definition of AIDS.

Person B. The pregnant spouse of A, a woman in her 20s, was found to be positive for the HIV antibody. In light of this information and the fact that one of her children (D) was positive for the HIV antibody, she elected to terminate her pregnancy. She named no sex partners other than her husband and had no other risk factors.

Person C. The son of A and B, in the 1- to 4-year age group, was negative for the HIV antibody.

Person D. The daughter of A and B, who was younger than 1 year, was reported positive for the HIV antibody. The patient was recently admitted to hospital for unremitting diarrhea of unknown cause.

Person E. A woman in her 20s, a sex partner of A, was found to be negative for the HIV antibody. The last exposure, according to A, was 1979.

Person F. This woman in her 30s, a sex partner of A, was negative for the HIV antibody. Her period of sexual exposure to A was 1983 to 1984.

Person G. This woman in her 20s, a sex partner of A, was reported positive for the HIV antibody. The last reported contact with A was during 1985. The contact allegedly occurred after the birth of child C but before the pregnancy that produced infant D. The patient said she did not use IV drugs or have a history of a blood transfusion. The patient's physician reported her as having unexplained lymphadenopathy in 1982. She elected not to identify her sex partners.

Person H. This woman in her 20s, a sex partner of A, has not been located. The last exposure was reported by A as 1980.

Discussion

Our goal is to prevent the transmission of HIV. Particular emphasis has been directed toward perinatal infections and unsuspected exposure among heterosexual women. A secondary objective is to educate seropositive persons on the meaning of their antibody status.

In the first group studied (Figure 1), one previously unrecognized infection in an infant was identified. We were successful in securing the release of this information to the infant's pediatrician. We believed that this would help the physician with the medical management should the infant become ill. In this cluster, A probably acquired her infection in the latter part of 1983, yet did not transmit the infection to the father of her third child, who had sexual exposure for at least 16 months.

It is not readily apparent when or how HIV was introduced into this cluster. Female O may have been exposed as early as 1981 while in New York but did not have contact with this group until 1984. Males H and G were probably infected before 1984 based on the available evidence.

In the second cluster (Figure 2) of our investigation, two previously unidentified cases of infection were detected. A man (C) in a well-defined high-risk group, who despite information from the Hemophilia Society had not been tested and had not been using preventive sexual methods, was advised of his antibody status and the potential for his transmitting HIV. He was referred to a physician familiar with hemophilia and HIV infections. He was also educated on the need to avoid other infections to reduce challenges to his immune system and avoid depleting his T-helper lymphocytes. The rationale for this advice was based on in vitro studies that show that activated lymphocytes are required for viral replication to take place.[16-20] If these studies prove correct, it follows that any behavioral change that would reduce the stimulation of his immune system might reduce the likelihood of AIDS developing.

An infected woman (E) in the second cluster was advised to defer pregnancy and referred to a physician knowledgeable about HIV and AIDS. The rationale for deferring pregnancy is twofold. Studies of small series suggest that infected, asymptomatic pregnant women are at increased risk for the development of AIDS or AIDS-related complex (ARC).[21] Second, we recommend deferral because despite the fact that the mechanism of perinatal transmission is unclear, it has been shown that 30% to 65% of neonates born to HIV-positive women are infected.[22-26] Our objective is to educate women of childbearing age so that they might choose to defer pregnancy until the perinatal transmission of HIV is better understood.

This cluster is also interesting in that male B was exposed to two infected women, yet has repeatedly tested negative over a six-month period. Testing began when his wife was diagnosed with ARC. There was no history of barrier contraception.

In the third cluster (Figure 3), we identified three previously unknown infections (B, D, and G). All three persons were referred to physicians familiar with HIV infections. The pregnant woman terminated her pregnancy based on her HIV antibody status and because her infant daughter was HIV-antibody-positive. Adult male A was educated on his potential ability to transmit HIV. Adult female G chose not to cooperate in any further aspects of this study, including preventive education.

It is unclear whether A transmitted the infection to G or the reverse. The information provided by A would suggest female-to-male transmission. However, G's reluctance to participate fully in the interview process has prevented confirmation of this.

In our investigations, the response to education on risk reduction among those found to be seronegative was varied. We noted profound concern among some patients and nonchalance among others. We stressed the use of condoms in interrupting the transmission of HIV, as in vitro studies have shown their efficacy.[27]

Conclusion

Based on these limited data, it appears that HIV may have been introduced into the San Bernardino area around 1983. Due to the long incubation period for AIDS,[28] it is often impossible to ascertain precisely the probable source of infection when numerous sexual and drug partners cannot be identified or located. We have elected to restrict future investigations to the period since 1983 and to easily locatable contacts only because the yield of infection among those located and tested in this study was high (12/34, 35%). This will serve to better utilize limited investigative resources.

Education targeted at specific groups and persons is the recommended method for the prevention and control of HIV infections. The chains of infection described show the need

for careful contact tracing and follow-up education. We have not provided evidence for the efficacy of such education, but believe it to be mandatory in the absence of a cure. It has been shown in our first and third clusters that the knowledge of one's antibody status can affect family planning decisions. Knowledge of asymptomatic infections will assist physicians in caring for patients. The documentation of transmission to new sexual or drug partners by seropositive subjects will enable disease control officials to determine that the infected persons have subsequently not changed their behavior enough to reduce the transmission of infection. For example, if C in cluster 2 or A in cluster 3 is associated with new infections, then it will be evident that educational activities have been less than optimal in their effect.

Current HIV antibody screening programs are voluntary and passive and are therefore unlikely to attract those persons who will have intimate contact with our subjects. The anonymous screening program attracts gay or bisexual men (36%) more than persons in other risk categories. Heterosexual women without other known risks comprise only 9% of those taking the tests since July 1985. It is hoped that the heterosexual persons who have been contacted by this study and found to be negative will in the future insist on the use of condoms for insertive sexual intercourse. While six cases of unsuspected infection were identified and education and referral provided, it cannot be stated that our efforts have interrupted the transmission of HIV or altered the behavior of those involved. That all patients with previously unidentified infections have complied with our medical referrals suggests some positive effect.

At present the law in California restricts the disclosure of HIV antibody test results for persons who do not have AIDS. As no cure or vaccine appears imminent, we believe these laws should be revised to provide safeguards regarding confidentiality while permitting the exchange of information among health professionals for the purpose of contact tracing and follow-up. The control of infectious disease has long been the responsibility of local health officers. In the absence of a satisfactory medical treatment, contact tracing coupled with education is indicated.

The community shares some responsibility as well. We suggest that the community equivalent of our public health control efforts would be to encourage anyone with a history of high-risk behavior to be tested. High-risk behavior would include unprotected sex between men, sharing of IV-drug equipment, receipt of blood or blood products since January 1977 and before May 1985, heterosexual relations with one of the aforementioned persons, the birth of an infant of infected parents, or having multiple heterosexual liaisons. This last category should be defined on the basis of the prevalence of the infection for a given area.

After testing, it is our hope that persons will act responsibly based on the knowledge of their antibody status. At the same time, health departments must be prepared with specific control procedures to deal with persons who show a disregard for their own health or the health of others. This can be handled with due respect for individual and community rights, as demonstrated in the past with other communicable diseases.

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The Role of Percutaneous Lung Biopsy in the Workup of a Solitary Pulmonary Nodule

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As the technique of percutaneous lung biopsy continues to evolve, it offers an increasingly accurate method of establishing the malignancy or benignity of a solitary pulmonary nodule. There are relatively few contraindications to the procedure, and the complications—primarily pneumothorax and hemoptysis—generally resolve without therapy. Transthoracic needle aspiration has an important role in the workup for a "coin lesion." Other elements of the diagnostic workup—particularly the history, a chest roentgenogram, computed tomography, sputum cytology, and transbronchial brush biopsy—may either add to or substitute for a transthoracic needle aspiration biopsy. An algorithm can be used to guide the diagnostic approach to a solitary pulmonary nodule.

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In 1983, more than 113,000 Americans died of primary carcinoma of the lung.[1] Most died within a year of diagnosis.[2] Lung cancer has been the leading cause of cancer death among American men for many years, and, by the mid-1980s, the disease showed it had "come a long way, Baby," by vying with breast cancer as the number one cause of cancer death in women in the United States.[1]

Some 5% to 15% of lung cancers present asymptomatically, usually being detected on chest radiographs.[2] The most common radiologic finding in these cases is the solitary pulmonary nodule, defined by Siegelman and co-workers as "a single rounded or ovoid lesion in the lung parenchyma which is not associated with obvious adenopathy, atelectasis, or pneumonia."[3] The differential diagnosis of the solitary nodule is extensive (see Table 1). What proportion of solitary lung nodules is malignant depends greatly on the criteria used for inclusion in a series. Lesions detected in mass screening programs may have a malignancy rate of only 3%; resected nodules have as high as a 60% rate of malignancy.[3]

Therein lies the dilemma: among the many patients with a solitary pulmonary nodule noted on chest radiograph, who should undergo thoracotomy? Investigators have developed several preoperative evaluations of the solitary pulmonary mass, with varying specificities, sensitivities, and predictive values.

In this article I will review these methods of assessing a solitary pulmonary nodule, but my discussion will focus on transthoracic needle aspiration biopsy.

The justification for such a biopsy is to prevent an unnecessary operation. The 1984 study by Keagy and colleagues shows that lobectomy and pneumonectomy—as well as minor resections—are frequently done for benign disease.[4] Steele's classic series of resected pulmonary nodules aptly shows the attendant risk of such an operation: he reported two perioperative deaths among patients with benign disease.[5]

I will discuss the balance between the risks of percutaneous lung biopsy—that of a missed diagnosis as well as risks of the procedure itself—and the benefits of the technique. I will also put transthoracic needle aspiration biopsy into perspective in the overall workup of patients who have a solitary pulmonary nodule.

Percutaneous Lung Biopsy

History

The first transthoracic needle biopsy was done in 1883 by Leyden, who sought to obtain microbes from a patient with pneumonia.[6] In 1886, Menetrier was the first to diagnose lung cancer from a transthoracic biopsy.[7] In the 1930s and 1940s, the procedure fell out of favor: the complication rate was high, and several deaths had occurred following percutaneous biopsy.[8]

During the 1960s, however, Dahlgren and Nordenstrom reawakened interest in the transthoracic biopsy.[9] The technique was considerably safer with the introduction of improved image-intensified fluoroscopy and narrow-gauge, thin-walled needles. Moreover, cytologists had refined their techniques, making the results of a percutaneous lung biopsy more accurate. In the past two decades the procedure has become increasingly popular.

Technique

A full description of the method of percutaneous lung biopsy has been provided by Greene.[10] Only general trends will be discussed here.

Beginning in the 1960s, improvements in cytology allowed fine-needle aspiration to replace large-bore cutting histologic biopsies with their attendant complications.[10] Moreover, recently investigators have developed thin needles that yield histologic as well as cytologic specimens. Westcott advocates the use of a slotted 20-gauge needle,[11] and Greene and associates recently published promising results using fine needles with circumferentially bevelled tips.[12]

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Percutaneous lung biopsy is generally done with fluoroscopic guidance, but computed tomography (CT) can occasionally play a helpful role. CT guidance is vital if either a pulmonary lesion is not visualized on both posteroanterior and lateral chest radiographs or a mass cannot be easily distinguished from normal hilar or mediastinal structures by using only fluoroscopy.[13] Moreover, CT may complement the use of fluoroscopy in the evaluation of a large chest mass, where CT images can help the fluoroscopist avoid a nonviable, necrotic—and thus nondiagnostic—portion of the mass.[14]

Having a pathologist present at the biopsy will increase both the accuracy and the safety of the study. He or she can do a "wet read" of the specimen and immediately decide on its adequacy,[15] thus avoiding unnecessary, numerous attempts. If the pathologist is familiar with the clinical history, mistakes such as confusing the sequelae of irradiation or chemotherapy with a malignant neoplasm can also be avoided,[16] thus increasing the specificity of the procedure.

Contraindications

Relative and absolute contraindications to a transthoracic needle aspiration biopsy include a bleeding diathesis or anticoagulation therapy; a possibility of the mass being a vascular lesion or an echinococcal cyst; severe obstructive or restrictive lung disease; local bullous lung disease near the target; pulmonary hypertension; an uncooperative patient or one with an uncontrollable cough; a patient either on or likely to soon require positive-pressure mechanical ventilation; and a contralateral pneumonectomy.[8,12,17,18]

Complications

The most common complication of percutaneous lung biopsy is pneumothorax. The incidence of pneumothorax ranges from 10% to 49%, but the rate of cases requiring therapy is much lower, usually between 4% and 10%.[8,10-12,17-22] A chest tube or an aortography catheter may be placed for a progressive or significant pneumothorax.[11]

The risk of pneumothorax is increased in patients older than 50 years, in patients who move or cough, if there is emphysema, if fissures are crossed, if the mass is central, or if the mass is cavitary.[15,19]

TABLE 1.—*The Differential Diagnosis of the Solitary Pulmonary Nodule*

- Malignant
  - Bronchogenic carcinoma
    - Epidermoid or squamous cell
    - Adenocarcinoma
    - Small-cell carcinoma
    - Large-cell carcinoma
  - Bronchial adenoma
  - Metastases
  - Other primary cancers
- Benign
  - Granuloma—including nonspecific inflammation, tuberculosis, cryptococcosis, histoplasmosis, aspergillosis, and other infections
  - Hamartoma
  - Bronchogenic cyst
  - Chronic pneumonitis or abscess
  - Benign pleural tumor
  - Bronchopulmonary sequestration
  - Nodular pulmonary amyloidosis
  - Neurogenic nodule
  - Rheumatoid nodule
  - Lipoma
  - Other benign tumors

The second common complication of percutaneous lung biopsy is hemoptysis. The incidence of hemoptysis ranges from 8% to 19%,[8,11,17,19] and the problem is generally minor and self-limited. Hemoptysis is more common after biopsies of central lesions.[19]

Fatal complications of percutaneous lung biopsy are rare. Greene estimated the mortality since 1970 to be "considerably less than 0.02%."[10] The use of thin needles has probably been critical in reducing the mortality, for before the 1960s, the most common cause of death from percutaneous lung biopsy was hemorrhage. The safety of thin-needle biopsy is shown by Westcott's report of four patients with thoracic aortic aneurysms simulating pulmonary masses that, following the biopsy of these masses, showed no radiographic or clinical evidence of hemorrhage.[11]

Air embolism is another potentially fatal complication, but this is rare. As of 1982, only one case of fatal air embolism had ever been reported.[10,23] The danger in doing a transthoracic needle biopsy is that only 2 to 3 ml of air is required to cause death in patients with pulmonary venous embolism. In his discussion, Westcott points out that there are two ways for air to enter a pulmonary vein during a percutaneous lung biopsy. The first is for atmospheric air to enter a pulmonary vein crossed by the biopsy needle. This can be avoided by having patients hold their breath whenever the stylet is uncovered. The second way is that a needle traversing a bronchus and a pulmonary vein can establish a tract between the two that may remain patent after the needle is removed, especially if the structures are rigid, such as in patients with extensive consolidation, abscess, or pleural disease.[23]

Another concern is the possibility of seeding malignant cells along the needle tract of an aspiration biopsy. As of 1985, however, there were only four known cases of tumor spread along "fine" needle tracts.[24] Greene recommends the use of coaxial introducing needles to reduce this almost theoretic risk.[10]

In summary, then, thin-needle aspiration biopsy of the lung is safe. The major complication is pneumothorax, and only about 10% of all patients require any kind of therapy following the biopsy.

Results

The results of eight series of transthoracic needle aspiration biopsies are shown in Table 2.

Probably the most important aspect of the percutaneous lung biopsy is its sensitivity for malignancy. Without sensitivities consistently near 100%, the specter of a missed malignant neoplasm looms large. The possibility that one will lose the chance to cure a patient of lung cancer is too great a risk for most clinicians and patients to take.

Various researchers have proffered suggestions on how best to avoid "false-negative" results. A common recommendation is the use of CT, particularly for large lesions, to decrease the chance of taking a biopsy of necrotic tissue in malignant tumors. CT can help a radiologist obtain material from the usually viable peripheral zone of a mass.[16,19,25,26] Westcott, moreover, cautions against doing a percutaneous lung biopsy in any patient with atelectasis or lobar consolidation,[11] for both he and others[17] have obtained spuriously negative results in cases where tissue distal to an obstructing bronchogenic carcinoma was taken instead of tumor. Both

TABLE 2.—*Results of Thin-Needle Aspiration Lung Biopsy*

Source	N*	Diagnostic Yield, %†	Sensitivity, %	Specificity, %	PV+‡	PV−§
Westcott, 1980[11]	400	100	98	96	99	95
Greene et al, 1985[12]	150	97	97	100	100	87
Khouri et al, 1985[17]	650	77	95	96	99	82
Lalli et al, 1978[18]	1,296	86	85	99	99	64
Berquist et al, 1980[19]	430	82	100	100	100	100
Landman et al, 1975[20]	80	100	89	100	100	88
Stevens & Jackman, 1984[21]	447	83	92	98	99	78
Dahlgren & Lind, 1972[25]	145	92	100	96	99	100

*N = the total number of biopsies done.
†The diagnostic yield refers to the number of biopsies judged "benign" or "malignant" versus the number done.
‡PV+ = predictive value of positive result.
§PV− = predictive value of negative result.

Westcott and Greene and co-workers advocate the use of histologic specimens to increase the chance of obtaining a specific, and therefore more reliable, benign diagnosis.[11,12] In addition, several investigators, such as Gobien and associates, encourage repeating an aspiration biopsy if the initial attempt yields insuffcent tissue for a specific pathologic assessment of benignity or malignancy.[26]

These measures notwithstanding, there will probably always be a risk of a missed malignant neoplasm associated with a percutaneous lung biopsy.

Competitors and Complements

The Initial Workup

History, physical, and laboratory evaluation. Any diagnostic workup begins with a history, and that of a solitary pulmonary nodule is no exception. Age is a critical factor in the risk of malignant solitary nodules: primary lung cancers are rare in persons younger than 30 years.[3,5,27] A smoking history increases the risk of malignancy.[3] A positive purified-protein-derivative test or a history of exposure to tuberculosis may support a benign diagnosis,[27] but neither excludes a malignant neoplasm. Indeed, the presence of active tuberculosis may increase the risk of concomitant malignancy: Gopalakrishnan and colleagues found a 90-fold increase in the incidence of lung cancer among their patients with tuberculosis compared with the general population.[28]

A patient who is symptomatic from a pulmonary nodule—the most common complaint is hemoptysis—is more likely to have a malignant lesion, as 80% to 85% of pulmonary masses causing hemoptysis are malignant.[3] It is rare, however, for a solitary pulmonary nodule—benign or malignant—to cause symptoms, and thus the lack of hemoptysis does not support a benign diagnosis.[27]

A history of prior malignancy increases the likelihood of a solitary pulmonary nodule being metastatic, but it does not exclude the possibility of a new primary or benign disease.[3,5] In Adkins and co-workers' series of 31 patients with a history of presumably cured cancers and a single pulmonary mass who underwent thoracotomy, only 22 patients had metastatic disease; 2 had new primary cancers, and 7 had benign disease.[29]

The physical examination is rarely helpful in assessing a solitary pulmonary mass except as it may reveal the source of metastatic disease. Similarly, laboratory tests in the workup of a solitary lung mass are most helpful if they uncover sources of metastases. Lawhorne and associates recommend measurements such as a hematocrit, liver function tests, analysis of urine, and a guaiac test of stool to help rule out extrathoracic primary lesions.[30]

Radiologic Assessment

Chest roentgenogram. The solitary pulmonary nodule, by definition, is a roentgenographic finding, and much information about the mass can be gleaned from the chest radiograph. Among the key elements in the radiographic assessment of a solitary lung mass are the presence of calcification, growth rate, contour, and size. Only the first two are reliable enough to exclude the presence of malignancy.[3,27]

Certain patterns of calcification in a nodule are reliable indicators of benignity. "Benign" patterns include laminated or concentric calcification (characteristic of granulomas), a central calcified nidus, "popcorn" calcification (typical of hamartomas), or homogeneous calcification.[3,27] These patterns are helpful, for calcification on a chest radiograph does not absolutely exclude malignancy. Generally, if a malignant nodule is calcified, it will show an eccentric pattern. Even with a "benign" pattern, however, most authors recommend follow-up chest radiographs at three to six months and yearly thereafter.[3,27]

The absence of growth of a solitary pulmonary nodule can also be used to establish benignity. If a lesion shows no change over the course of two years, it is benign. Yearly follow-up chest radiographs are still recommended, however.[3,27]

The contour of a pulmonary nodule can be suggestive of malignancy or benignity. Generally, an irregular contour, a spiculated border ("corona radiata"), and ill-defined margins argue for malignancy; smooth edges support a benign diagnosis.[3,27,31] A lobulated or umbilicated contour is usually a result of differential growth rates at the periphery of a lesion and is characteristic of malignancy. Lobulations may also be seen, however, in patients with tuberculosis or hamartomas.[27] Thus, the contour and margin of a lesion should not be used in isolation to assess its malignancy.

Likewise, the size of a lesion may be suggestive—but not diagnostic—of malignancy. Lesions greater than 3.5 cm in diameter are usually malignant.[3,31] Small nodules tend to be benign, but once a lesion has passed the radiographic threshold of about 1 cm, there is too much overlap between malignant and benign lesions to warrant delaying surgical excision or another diagnostic procedure on the basis of size.[27]

Tomography and CT. In the past, conventional tomography has been used both to increase the detection of calcification in a lung nodule and to visualize any additional nod-

ules.[32] In recent years, however, more researchers have been focusing their attention on CT.

In the past decade, the role of CT in the workup of solitary pulmonary nodules has been continually changing. A 1978 study by Raptopoulos and associates of solitary pulmonary nodules assessed with CT was promising in detecting calcification in benign lesions.[33] Subsequent attempts to confirm the usefulness of CT in this role met with mixed success, however.[27] The major pitfalls are well outlined by Godwin[27] and include the technical differences among scanner models and even among different machines of the same models.

Thin-section CT and improvements in standardization have helped solve some of these problems. The development of a reference "phantom" has finally allowed studies of CT densitometry independent of variations among scanners.[14,31] The initial results are promising and indicate that in small nodules (<3 cm), CT can greatly enhance the ability to establish a benign diagnosis.[31] The criteria for benignity currently used are high attenuation values—exceeding critical levels and distributed throughout the CT section through the center of the lesion—and a well-defined edge.[14] How great a role CT will have in assessing solitary pulmonary nodules remains to be seen. At the moment, it promises the ability to firmly and objectively establish a benign diagnosis, but only in a select group of nodules: small lesions with calcification and smooth margins.

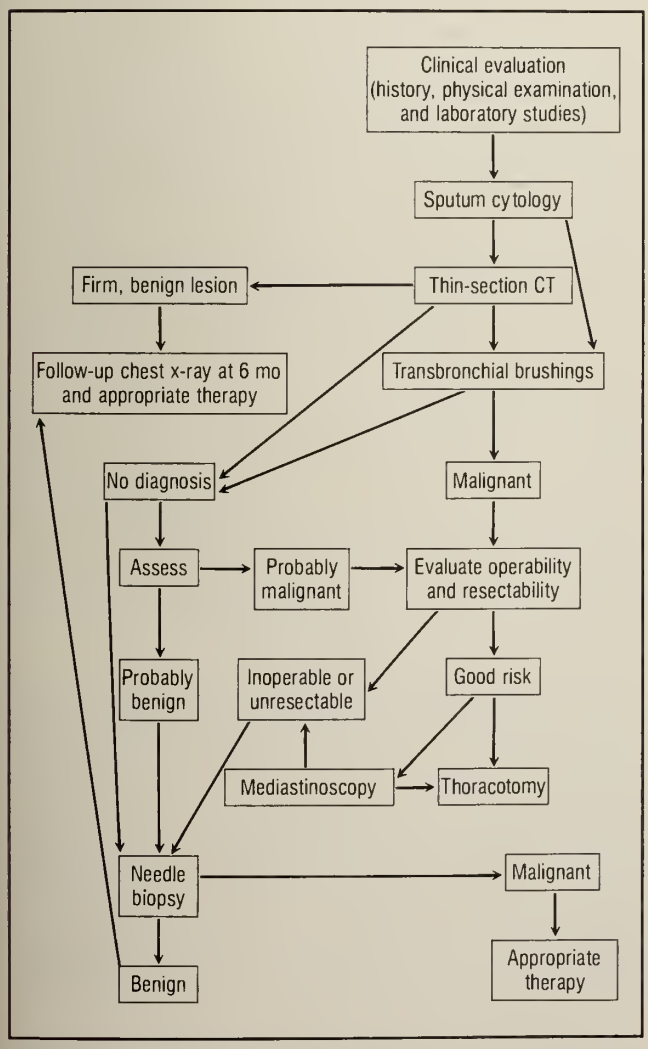

Figure 1.—The algorithm shows the steps to be taken when evaluating a patient with a solitary pulmonary nodule. CT = computed tomography

Other radiologic evaluations. A recurring question in the workup of solitary pulmonary nodules is what effort should be made to completely rule out extrathoracic cancers. In the absence of a histologic diagnosis, is a preoperative upper gastrointestinal series, barium enema, or an intravenous pyelogram called for? Lawhorne and colleagues reviewed the literature and found that less than 2% of solitary pulmonary nodules represent metastatic disease from occult cancer sites.[30] Thus, they concluded that these additional radiologic examinations are not indicated.

Sputum Cytology

The findings of sputum cytology are rarely diagnostic in the evaluation of a solitary pulmonary nodule.[27] False-positive tests are relatively common in the presence of inflammatory disease.[25] Moreover, a negative study is of questionable value: Dahlgren and Lind reported a test sensitivity of only 40% among 125 patients assessed with sputum cytology before thoracotomy for a single lung nodule.[25] When three consecutive sputum specimens were collected, however, the sensitivity for malignancy rose to 80%. The flaws of sputum cytology notwithstanding, its primary value is as a screening tool, for it is one of the cheapest and least harmful methods of detecting lung carcinoma.

Transbronchial Brush Biopsy

Transbronchial brushing is a noninvasive procedure with almost no complications. Generally, transbronchial brushings will be diagnostic more often than sputum cytologies but not as often as transthoracic needle aspiration biopsies.[10,20,27]

Landman and co-workers reported a test sensitivity of 72% overall among 100 patients with transbronchial brush biopsies.[20] Their success was almost entirely with centrally located bronchogenic carcinomas, of which transbronchial brushings detected 80%. Their transbronchial examinations were uniformly negative for malignant neoplasms other than bronchogenic carcinoma. Walls and associates similarly reported the complete failure to diagnose Pancoast tumors with bronchoscopy and washings,[22] compared with a test sensitivity of 100% for transthoracic needle aspiration biopsies of Pancoast tumors.

Transbronchial brush biopsy is most useful for diagnosing centrally located bronchogenic carcinomas.[20] The test sensitivity of percutaneous lung biopsy, however, is much greater than that of transbronchial brushings if a lesion is less than 2 cm in diameter; peripherally located; arises in the upper lobes; and does not arise in bronchial epithelium, such as in metastatic disease.

The Role of Percutaneous Lung Biopsy

The Workup of Undiagnosed Solitary Pulmonary Nodules

Researchers have yet to reach a consensus regarding the role of transthoracic needle aspiration biopsy in the assessment of the solitary pulmonary nodule. The algorithm shown in Figure 1 attempts to reconcile some of the evidence known to date.

The following points regarding the algorithm should be kept in mind (Figure 1):

- CT will probably not be helpful if the lesion is larger than 3 cm in diameter or has an irregular border.[31]

• Transbronchial brushings will contribute little if the lesion is less than 2 cm in diameter, peripheral, in the upper lobes, or likely to be metastatic.[20]

• In inoperable or unresectable cases, a histologic diagnosis offers both a confirmation of malignant disease and necessary data for irradiation or chemotherapy.

• The leap from no preliminary diagnosis to a needle biopsy remains a controversial step. Workers in the field have varying opinions, ranging from the thinking that percutaneous lung biopsy is "not appropriate for operable patients with strong evidence of malignant lesions"[27] to the claim of Lalli and co-workers that "a clear indication" for transthoracic needle aspiration biopsy is "the presence of a nodular lesion anywhere in the lung of a surgical candidate suspected of having a bronchogenic carcinoma," and that, in such cases, a thoracotomy is "indefensible."[18]

The lack of consensus around the last step represents a fundamental weakness of algorithms—that medicine cannot be practiced by flow charts.

Other Indications for Transthoracic Needle Aspiration Biopsy of a Solitary Lung Mass

A patient with a solitary pulmonary mass thought to be probable metastatic disease. In a patient with suspected cerebral or symptomatic bony metastases, a diagnosis of bronchogenic carcinoma is considered sufficient to begin radiation treatment to these lesions.[8,32]

A patient with a solitary mass and a known extrathoracic primary cancer. If CT shows that in such cases a lung nodule truly is solitary, then a needle aspiration biopsy is called for to rule in or rule out metastatic disease. Granted, the study of Adkins and associates showed an increased survival among such patients with extrathoracic cancer undergoing thoracotomy whether their solitary pulmonary nodule represented a new primary or metastatic disease.[29] Thus, some would argue that these patients do not benefit from a percutaneous lung biopsy but should instead proceed directly to thoracotomy. Stitik points out, however, that a diagnosis of metastatic disease is helpful,[8] for it allows the physician to intensify a search for other metastases before subjecting the patient to a surgical procedure.

A patient who refuses surgical treatment for a solitary pulmonary mass probably due to cancer. In the case of a resectable lesion in an operable patient who refuses an operation, a histologic or cytologic examination is needed for appropriate irradiation or chemotherapy. Moreover, a diagnosis of malignancy may spur such a patient to a surgical excision.[8]

A patient with a superior sulcus (Pancoast) tumor. Hilaris and colleagues are among the investigators who have shown that preoperative radiation therapy for Pancoast tumors improves patients' survival.[34] Particularly considering the low test sensitivity of sputum cytology and transbronchial brush biopsy in the diagnosis of apical lung cancer,[22] transthoracic needle aspiration biopsy is helpful in such cases.

Undiagnosed lung lesions in the immunosuppressed. In immunosuppressed patients with a solitary pulmonary nodule, opportunistic organisms or common bacterial pathogens can be specifically identified by a needle aspiration biopsy.[10] Not only does a swift diagnosis hasten vital therapy, but also these patients are often debilitated and may be only marginally operable.

Conclusion

It can be seen, then, that transthoracic needle aspiration biopsy does have a role in the workup of a solitary pulmonary nodule. Clinicians vary greatly, however, in how they limit that role. In some cases, such as an inoperable patient with a likely malignant lesion and normal results of a transbronchial brush biopsy, authors are in agreement that percutaneous lung biopsy is called for. Over a similar lesion in an operable patient, however, there is great dispute.

Surely the role of needle aspiration biopsy will continue to evolve. Standardization and further refinement of CT technology promises to eliminate some of the demand for a cytologic diagnosis by providing firm benign assessments. Improvements in cytology may increase the now low sensitivity of sputum cytology and transbronchial brush biopsies, thereby eliminating the need for an aspiration biopsy. On the other hand, improvements in cytology and other fields may increase the use of the percutaneous lung biopsy. Advances in cytology have allowed thin-needle aspiration, a much safer procedure than cutting needle biopsies. The promise that percutaneous lung biopsy offers is of a safe, relatively inexpensive, and increasingly reliable diagnosis. Some authors argue that even in an operable candidate, a malignant diagnosis has value insofar as it speeds a patient to surgery.[8,35]

But all clinicians can see the merit in a reliable, preoperative benign diagnosis. By preventing an unnecessary thoracotomy, morbidity and mortality are considerably reduced. Moreover, now that percutaneous lung biopsies may be safely done on an outpatient basis, the monetary savings are considerable: Stevens and Jackman estimated that the cost of a needle aspiration biopsy of a solitary lung nodule done on an outpatient basis was $382, whereas the bill for a diagnostic thoracotomy with a five-day hospital stay came to $9,000.[21] Other authors report great savings even in inpatient settings.[34] These savings may well drive institutions to change their patterns of care, and the use of such techniques as needle aspiration biopsy depends a great deal on institutional policy and referral patterns.[8]

Ultimately, however, the decision to use and to trust the findings of a transthoracic needle biopsy of a solitary lung mass is not an institutional one, but a personal one, made by the clinician, the radiologist, and the patient. Their ability to tolerate uncertainty will determine that decision. No flurry of studies or statistics, ledgers, or litigation will change the approach to the "solitary pulmonary nodule" from being an individualized decision, made anew with every case.

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Microbial Keratitis From Contact Lenses

DO YOU KNOW how many Americans are out there wearing contact lenses? It's about 8% to 10% of the population of this country. That's over 20 million Americans. I mean, if only .001% of those patients were getting this complication, that's thousands of people at risk of getting a corneal infection as a principal complication of contact lens wear.

In the literature, thousands of cases of corneal infections in contact lens wearers have now been reported. In Houston, the leading cause of corneal infection is contact lens wear.

What about the contact lens type? Hard lenses, daily wear, extended wear, and therapeutic lenses are the four choices we've got. Almost all cases that have now been reported are in soft contact lenses. The type of lens—the type of plastic—really seems to be a principal risk factor.

I did a literature survey and found 500 culture-proved cases and mapped those out with regard to the type of lens the patient was wearing when a corneal infection, culture-proved by corneal scrapings, was reported. Three fourths were wearing soft lenses, two thirds were wearing soft lenses for cosmetic reasons—they had 20/20 vision. Over a third were wearing extended wear lenses.

I've come up with some ways to prevent the problem—and unfortunately, they're not very innovative. They are things you're probably already doing and recommending, but let me just reiterate:

- Wash hands. I think, obviously, all eye care persons should wash their hands before manipulating any patient's eyes and before any eye examination or contact lens insertion. Patients should wash their hands before each contact lens manipulation as well.
- Remove that lens regularly. The patient should remove daily wear lenses in a daily wear schedule and clean and disinfect those lenses routinely. Obviously, here's a problem with patient compliance in a large number of cases.
- Use clean accessories. About a quarter of the cases have been traced back directly to contaminating organisms in the contact lens case and solution. Examine the lenses for spoilage at each eye checkup. And then lastly, reinstruct the patients periodically. This may be *the* most important and the best way we have of preventing this problem in our patients.

—KIRK R. WILHELMUS, MD

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Medical Progress

Adolescent Idiopathic Scoliosis

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Adolescent idiopathic scoliosis is the single most common form of spinal deformity seen in orthopedic practice. Our knowledge about the epidemiology, etiology, natural history, and treatment has recently increased dramatically. The incidence of small curves is rather high (2% of the population), whereas severe curves are much less common (< 0.1%), but we cannot always predict which curve will progress. Abnormalities of the neuromuscular system and of calcium metabolism, and certain growth, genetic, and mechanical factors may all play roles in the pathogenesis of the disorder. The physiologic secondary effects of severe scoliosis relate to restrictive lung disease, but most patients do not have a deformity great enough to affect their cardiorespiratory function. The psychological and social effects of scoliosis are significant for patients but difficult to quantitate. For most patients with moderate scoliosis—that is, more than 25 to 30 degrees—treatment with an underarm brace or electrical stimulation is adequate to "control" progression of the curve. Surgical fusion allows actual correction of the curve but is indicated in only a small percentage of patients—usually those with more than 50 degrees of deformity.

(Rinsky LA, Gamble JG: Adolescent idiopathic scoliosis. West J Med 1988 Feb; 148:182-191)

Scoliosis is a lateral curvature of the spine. A frontal plane curvature is the most obvious finding on anteroposterior radiography, but this is only one component of a three-dimensional torsional deformity of the entire torso. Rotation, sagittal-plane deformity, and rib changes also occur. Scoliosis is structural when part of the curvature is fixed. Idiopathic scoliosis is a structural curvature for which there is currently no known underlying cause. Arbitrarily, idiopathic scoliosis is divided into three groups by the age of presentation: infantile (0 to 3 years), juvenile (3 to 10 years), and adolescent (greater than 10 years). Adolescent idiopathic scoliosis is by far the most common.

Over the past 20 years, knowledge of adolescent idiopathic scoliosis has increased exponentially, specifically its epidemiology,[1-8] etiology and pathogenesis,[9-32] natural history,[33-44] and treatment.[45-63] Many of these "new facts" are controversial or even contradictory, clearly indicating that an understanding of the disorder is far from complete. We now recognize that much of the treatment in the past was unnecessary; not every curve needs treatment.[16,63] Also, scoliosis is probably the common phenotypic expression of more than one condition. Finally, school screening, while valuable,[64,65] can be a double-edged sword, offering both advantages and disadvantages to practitioners.[1,66,67]

Diagnosis and Epidemiology

Scoliosis may be diagnosed by examining the contour of the back in the standing and 90 degrees forward-flexed position. A rib or loin hump is the best indication of an underlying scoliotic deformity[63]; measuring the distance from the arms to the trunk is also a useful screening technique. The scoliosis is described by the direction of the frontal-plane convexity and the position of the apex vertebrae. The four most common patterns of curvature are remarkably consistent: more than 90% of single thoracic curves are to the right, 80% of thoracolumbar curves are to the right, more than 70% of single lumbar curves are to the left, and 90% of double major curves are right thoracic and left lumbar. The appearance of a left primary midthoracic curve is unusual enough to alert a clinician to a possible underlying neurologic or neoplastic cause. Spinal curvatures are measured by the Cobb technique, which measures the angles subtended by the end plates of the highest and lowest vertebrae within the curve (Figure 1). Unfortunately, small degrees of rib and scapular asymmetry or inequalities of shoulder and waist height are common in normal people,[1,2,68] at times leading to overdiagnosis and needless radiographs.

Bunnell, in an effort to decrease x-ray exposure, has devised a simple device called an inclinometer that compares the horizon of the back with the horizontal plane in the forward-flexed position.[45] This test is suitable for mass screening because it is sensitive, reasonably specific, and takes less than 30 seconds per child. Any tilt of less than 5 degrees does not usually require a radiograph, as the Cobb angle is likely to be less than 20 degrees.

Attempts have been made to determine the incidence of scoliosis in the general population by using clinical examination,[4-7,64] moiré photography,[1] spinal radiographs,[4] and reviews of miniature chest radiographs.[8] Reported incidences vary widely depending on the strictness of the criteria used, the population age screened, and the skill of those screening. The earliest statistical studies (from a review of 50,000 miniature chest films in Delaware) detected an incidence of 1.9% of 10-degree or greater curves in the population older than 14 years. Several studies of screened school children in the United States, Canada, the United Kingdom, and elsewhere have generally confirmed a curvature incidence of about 2%[63] if the criterion of greater than 10 degrees is used. If

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ABBREVIATIONS USED IN TEXT

AP = anteroposterior
CNS = central nervous system
CTLSO = cervical-thoracic-lumbar-sacral orthosis
EMG = electromyography/-ic

curves between 5 and 10 degrees are included, then the incidence is much higher at 4% and 13.6%.[3,6]

It is rather zealous to consider as "abnormal" the large number of children with a 5- to 10-degree curve. Of curves less than 10 degrees, 90% never progress (or even regress), and they are totally without cosmetic or physiologic significance; it seems best to consider these lesser curves simply as normal variants. A few of the 10-degree curves are important in that they will subsequently worsen, but most are insignificant. The incidence of curves greater than 20 degrees is only 0.2% to 0.3%.[63]

These large population studies have greatly increased our knowledge of the distribution and magnitude of spinal curves. For example, adolescent idiopathic scoliosis has long been known to affect predominantly girls. With decreasing curve severity, however, the female-to-male preponderance tends to decrease. Thus, for 10- to 20-degree curves, the girl/boy ratio is 2:1, whereas for curves greater than 30 degrees, the ratio is 10:1.[63] The overall incidence of severe curves (greater than 40 degrees) involving cosmetic and physiologic concerns is quite low at much less than 0.1%. Many mild curves will spontaneously improve or even resolve.[5,6]

Much of the epidemiologic information comes from school screening programs, mandated by law in a number of states. School screening was initiated because it seemed axiomatic that earlier diagnosis would result in less treatment, save money, and eliminate the need for surgical treatment. Early studies seemed to indicate that a trend of decreased surgery and improved cost-effectiveness was the case.[64,65] School screening has increased the general level of awareness and basic knowledge about scoliosis within the medical community. By realizing that most curves of less than 20 degrees do not progress, we can eliminate these children from our treatment protocol, be more realistic in our evaluation of new treatment, and are less likely to overtreat. Additionally, screening programs have increased the public awareness of scoliosis. Finally, a few cases of significant scoliosis will be picked up early and perhaps prevent the necessity of surgical repair. School screening, however, is now recognized to have advantages and disadvantages.[66,67] What, then, are the risks and benefits of a school screening program?

Figure 1.—The photoradiograph is of a 12-year-old girl with a (Cobb) 50-degree right thoracic curve, progressive despite bracing. Note breast shields. Even larger shielding is now recommended.

The assumptions underlying any recommendation for a mass screening program are threefold: (1) The screening program should identify most positive cases (accurate tests), (2) the screened condition is intrinsically harmful or will become so if untreated, and (3) an available and effective treatment exists that will change the natural history of the condition once the condition is identified.

There are enough disadvantages to initiating a school screening program that some question the benefits of widespread school screening except as a research epidemiologic tool. First, there are many falsely positive cases[2,4,5,68] due to the large number of children with asymmetry of shoulder height, rib prominence, or pelvic shape. These children and their parents will be needlessly alarmed and the children perhaps exposed to radiation. Second, the vast majority of those screened and found to actually have a curve will not have a progressive curve and will not benefit from or need treatment. They will have also been needlessly alarmed and possibly subjected to radiographs. Armstrong and co-workers noted that only 10% of those subjected to radiographs were even close to the range where any treatment would be considered.[2] In a more recent study from China, of 8,165 children screened, 790 had abnormal results, and nearly all of them underwent radiography; 171 had curves greater than 10 degrees, but only 10 children had curves greater than 20 degrees (0.1%).[5]

Perhaps more important, there is no universally accepted nonoperative treatment that has been proved to alter the natural history. Orthotic bracing and electrical muscle stimulation programs are now widely prescribed and accepted by the general medical community, but unequivocal, nonbiased proof of efficacy of the treatment of scoliosis by nonoperative means is lacking.[58] Exercise alone does not halt the advance of progressive scoliosis.[47,54] Many studies report the efficacy of one type of brace or another, but these studies vary in methodology, patient population, selection criteria, and outcome evaluation. Historical controls do not serve as an accurate standard for comparison. In one of the few nonoperative, prospective, controlled evaluations, Miller and associates found no major statistical difference in the outcome between braced and nontreated groups.[58] Although most orthopedic surgeons believe that orthotic treatment is effective,[46,48,50,51,56,62,69] it still remains to be proved just how effective and in which patients it should be best used.

Thus, school screening programs may lack accuracy and result in unnecessary referrals. Whether these programs result in fewer operations is moot. Although the American Academy of Orthopaedic Surgeons still recommends school

screening, questions remain. Several recent authors have questioned the usefulness of school screening programs and recommended that they be continued mainly as a research tool.[66,67] Even using adjunct methods of evaluation such as moiré photography,[1] large numbers of false-negatives and false-positives remain. Despite the worthy goal of early identification, school screening for scoliosis does not meet the above criteria outlined for mass screening.

Radiographs are necessary to rule out intrinsic vertebral deformities (congenital curvatures) or other vertebral pathology, but radiation exposure should always be minimized. Exposure to the skin from one anteroposterior (AP) projection can range from 25 to more than 1,000 mrem.[59,70] Decreasing the frequency of radiographs is obviously the easiest and most direct way to cut exposure. A single standing AP radiograph is usually all that is needed for a screening film. Bending films and other special views are appropriate for planning surgical correction, not for screening. Taking the film posteroanterior[59] rather than AP cuts down the exposure to the breasts and thyroid; the use of lead breast and thyroid shields cuts the exposure in AP views. High-speed film-rare earth screen combinations, collimation, gonadal shielding, and compensating filters also decrease radiation exposure. Follow-up films should usually be taken no more than every six months and can be alternated with other techniques such as moiré photography. Underpenetrated or overpenetrated films in follow-up should usually be accepted and not repeated if they show the outlines of vertebral bodies.

Etiology and Pathogenesis

The etiology and pathogenesis of scoliosis are not the same. For example, in neuromuscular ("paralytic") scoliosis due to polio, the cause is infection by the poliovirus. The pathogenesis, however, involves anterior horn cell destruction, muscle imbalance, and biomechanical plus growth changes of the spine that remain obscure. Both the etiology and pathogenesis remain obscure in adolescent idiopathic scoliosis.

Recent literature on the etiology shows central nervous system defects,[21,22,26,27] faulty collagen biochemistry,[71] abnormal proteoglycans,[19] and aberrant muscle physiology.[23,28,72] These patients reportedly grow too quickly,[73-75] have poor proprioception,[21,22,24] and have abnormal platelet function.[14,29] Current theories relate to the general classes of genetic factors; hormonal and growth-related factors; biochemical abnormalities; abnormalities of skeletal muscle; and basic abnormalities of platelet and calcium metabolism and of the central nervous system, especially vestibular abnormalities. How can such diverse theories of etiology be reconciled?

First, we must recognize that idiopathic scoliosis is probably not a single disease, but rather, like emphysema, is the final common pathway of a number of disorders. Second, many studies to date have lumped different patients into study groups with varying degrees of severity, ages, and so forth.

Genetics seems to play a significant role in the causation of adolescent idiopathic scoliosis.[11,25,76] Familial occurrence is a common clinical observation, particularly with mothers and daughters. In one large family study, Wynne-Davies concluded that the disorder was due either to a dominantly inherited single gene or, more commonly, multiple genetic factors.[25] Others have suggested that the overall female preponderance indicates X-linked dominance inheritance.[16,76] Scoliosis is commonly seen in single gene disorders of connective tissues such as Marfan's syndrome, the Ehlers-Danlos syndrome, and osteogenesis imperfecta. Each of these syndromes is heterogeneous with a number of genetic subgroups, and each is relatively rare. The carrier frequency of the heterozygote state, however, even for the rare, often recessively inherited disorder, is high. For example, if the *disease* frequency of a recessive disease is 1:40,000, then the frequency of the *carrier* state is 1:100 in the general population. It may be that heterozygosity for one or more of the collagen defect genes is a factor in many "idiopathic" cases.[11] Investigators have studied collagen stability and cross-linking in skin and intervertebral discs. Francis and colleagues analyzed the collagen of skin biopsy specimens from 15 patients with adolescent idiopathic scoliosis and found collagen more readily dispersed (less stable) in scoliotic patients.[71] They proposed that there might be defective cross-linking of the collagen fibers. Parsons and co-workers reported abnormalities in the collagen content of the intervertebral discs in patients with the disorder.[18] Collagen was more concentrated in the nucleus and the convex portion of the annulus, and there was an imbalance in the ratio of type 1 and type 2 collagenous fibers between the convex and concave portions of the disc. These differences of disc collagen most likely are the result of the spinal deformity rather than causative.

Comparisons of normal and scoliotic discs have shown differences in the proteoglycan and hyaluronate composition of aggregates and nonaggregating monomers.[17,19,77] No difference between discs from the spines of patients with adolescent idiopathic scoliosis versus discs from scoliotic spines due to cerebral palsy was found. This suggests that the curvature per se may lead to alterations in proteoglycan composition rather than there being a primary biochemical alteration.[17] Hormonal and growth factors have also been investigated with a similar difficulty in relating "positive" findings to cause versus effect.[16,73-75,78-80]

Well accepted is the observation of a rapid increase in curvature during the adolescent growth spurt. This is the time when a child with idiopathic scoliosis is at most risk. Not so well known is that the standing torso length of girls with scoliosis is slightly longer than that of controls, suggesting that the increased growth also places them at increased risk. This is further reinforced by the finding[74] that the growth spurt occurs a year earlier on the average in girls with the disorder than in controls. Continued progression of the curve after the slowing of the growth rate may occur because once a curve has reached a certain critical degree, gravity and mechanical factors make the progression autonomous of biologic factors.[81]

The direction of vertebral rotation (in the transverse plane) is consistently into the convexity. This has the net effect that the anterior column is relatively too long compared with the posterior bony elements. Thus, a scoliotic spine has an obligatory lordosis due to the anterior-posterior length imbalance.[12,79,82] This fact correlates well with the observation that right thoracic curves have a decreased kyphosis or even a true lordosis on a standard lateral radiograph. Dickson and co-workers suggested, however, that if a true lateral x-ray film is taken of the apical portion of the curve—which by definition will need to be taken oblique to the usual lateral x-ray film—*all* idiopathic scoliosis will be found to be lordoscoliosis.[12] The apparent "kyphosis" with scoliosis is due to rota-

tion and our inability to accurately conceptualize the spine three-dimensionally.

Lawton and Dickson have further confirmed this "rotated lordosis" concept with an experimental model in rabbits in which they successfully produced idiopathic-appearing curvatures only after causing both unilateral soft tissue instability and lordosis (by tying two spinous processes together with sutures).[82] Even more dramatic was the fact that if the lordosis-producing sutures were divided before the scoliosis became too severe, the curve would improve as long as growth remained. From these data the vertebral anomalies in adolescent idiopathic scoliosis were hypothesized to be related to an imbalance between the posterior and anterior growth rate with relatively excessive anterior growth.

Abnormalities of skeletal muscle have been found in many studies of the disorder.[10,23,28,30,72] This search seemed reasonable because muscle weakness (especially polio) is a known precursor of scoliosis. (During the era of a high incidence of polio, adolescent idiopathic scoliosis was thought to represent subclinical cases of polio.)

Electromyographic (EMG) analysis can be done of the spinal or extremity muscles, and biopsy and histochemical studies can be done at the time of surgical correction. More theoretically desirable would be biopsy specimens of muscles of the extremities (such as the deltoid)[28] to avoid sampling errors induced by the deformity itself. Muscle strength has also been objectively tested.[15,20] Unfortunately, no two studies involve comparable patient populations, such as the degree of scoliosis, sex distribution, and the like, or the same method of evaluation, so it is difficult to compare results. Most biopsies have involved patients with scoliosis already severe enough to require operation.

In general, studies have shown type 1 fiber predominance on the convex side.[16,23,30,72] It is not clear whether this is primary, secondary, related to an increase in type 1 fibers, or atrophy of type 2 fibers. Ultrastructural changes have included derangements of myofilaments and Z-band streaming, as well as changes in lipid and glycogenic content of the involved muscle. These findings may represent a physiologic adaptation of the paraspinous muscles to the altered biomechanics[30]—as if the convex side muscle is undergoing "endurance training."

Yarom and associates favor a generalized disorder of all contractile protein as a cause of adolescent idiopathic scoliosis.[28,29] In their histographic analysis of deltoid muscle, a consistent "hypotrophy" of type 1 fibers on the concave side was found. There was also EMG evidence of myopathy of the deltoids especially noted on the concave side. This muscle would not be expected to be involved by any secondary effects from the deformity. The reasons for the asymmetric findings remain hypothetic but were considered possibly related to asymmetric proprioceptive or other abnormal primary neurologic input.

Despite all of the above evidence for subclinical myopathy, the patients with idiopathic scoliosis have normal strength on clinical examination. Even detailed sophisticated, objective measurement of trunk strength has not shown any difference between scoliotic patients and normal controls.[20] In summary, despite many histochemical, ultrastructural, and EMG abnormalities of muscle, a primary deficit in adolescent idiopathic scoliosis remains to be proved. A mild, nonprogressive, congenital myopathy possibly induced by some central nervous system (CNS) abnormalities is hypothesized by many.

Perhaps related to abnormalities in muscle are abnormalities of platelet contractility and calcium metabolism. Floman and colleagues found impaired platelet aggregation, impaired platelet release of serotonin, and abnormal synthesis of thromboxane A_2.[14] Elevated levels of intracellular calcium in the platelets of patients with scoliosis were noted by Yarom and co-workers.[29] The platelet functional anomaly is not associated with prolonged bleeding times, spontaneous hemorrhage, or excess bleeding during a surgical procedure. Investigating platelet abnormalities has the theoretic advantage that an abnormality found is likely to be primary, not secondary to the curve itself.

The most "popular" etiologic factors are CNS abnormalities, especially related to balance, proprioception, and the vestibular system.[16,21,22,24,26,27] Scoliosis is seen commonly in patients with overt or diffuse CNS disease, for example, cerebral palsy and Friedreich's ataxia. Yamada and Yamamoto and associates hypothesized a functional impairment in the postural regulatory mechanisms between the brain-stem centers and the proprioceptive afferent pathways.[26,27] These tests included vestibularily generated eye movements (by rotating blindfolded subjects), visually generated eye movements (by having subjects watch a metronome), and tests of equilibrium dysfunction. Equilibrium dysfunction was found in 80% of scoliotic patients on at least one test versus only 5% of controls. Similar dramatic results have been reported from Sweden by Sahlstrand and colleagues.[21,22] They also noted an increased incidence of electroencephalographic abnormalities in the idiopathic scoliotic population, as well as faulty equilibrium responses by stabilometry testing of the instant center of gravity. This suggests that the scoliotic patients were subclinically ataxic. Wyatt and associates found alterations in vibratory sensibility and proprioception in patients with idiopathic scoliosis.[24]

Stable balance is a very complex phenomenon involving brain-stem integration of input from visual, proprioceptive, and vestibular sources. Subtle defects in any of these pathways could well exist but are far from being proved as universally causative of adolescent idiopathic scoliosis for the following reasons:

- Most of the studies included heterogeneous population groups. Is it fair to compare a 15-year-old who has a 20-degree curve with a 12-year-old with a 60-degree curve?
- In every "positive" study, many—at least 20% of the scoliotic patients—had normal balance even on the index test.
- Some of the findings are paradoxically opposite. For example, whereas scoliotic patients are alleged to have decreased proprioceptive sensibility, the same patients had *increased* sensitivity to vibration.[24] This occurs despite the fact that both sensations are carried by the posterior columns of the spinal cord.
- In our own study using a computer-controlled stabilometry platform,[1] scoliotic girls were at least as stable if not more so in standing than the normal age-matched controls. Driscoll and co-workers used a clinical battery of tests developed by the National Aeronautics and Space Administration of seven subtests to measure static and dynamic equilibrium.[13] They also found no difference between patients with scoliosis and controls.

In summary, our clinically healthy scoliotic patients have had a tremendous number of "abnormalities" found despite the fact that they seem neurologically normal, have normal muscle strengths, do not bleed excessively, and do not have overt defects of connective tissue.

What can be stated categorically is that genetics plays a significant role; likewise, growth and mechanical factors also play a role, especially when the curve reaches a certain critical size. There are suggestions of asymmetries in the neuromuscular system that may or may not be primary. Abnormalities of calcium and contractile elements are intriguing but need further investigation, particularly in studies comparing homogeneous groups. The condition of scoliosis is best considered as a final common outcome of the growing spine due to multifactorial causes.[16]

Natural History

If a specific treatment of scoliosis is to be evaluated, then the natural history of scoliosis in untreated children and adults must be known. The natural history may be evaluated in different ways with regard to the chance of progression (worsening), secondary complications such as back pain and decreased pulmonary function, psychosocial and self-image problems, and premature mortality. Unfortunately, reported series have lumped together scoliotic patients with widely varying curve locations, degrees of severity, and even causes. As a result, patients with moderate lumbar curves may be needlessly alarmed about possible decreased pulmonary function, ability to work, pregnancy, or early mortality.

The analysis of curve progression focuses on two issues: What is the chance of progression of a curve before the cessation of growth—that is, the possible time period of conservative treatment? What is the chance and likely rate of future progression in a mature patient? Most mild curves (less than 15 degrees) in growing children do not significantly increase, and some curves (under 20 degrees) will even spontaneously resolve.[3,5,63,66,67] The information available for a likelihood of curve progression relates primarily to girls because the overall percentage chance for an increase in girls is much higher than in boys.[63,66,83] Furthermore, what must be clearly understood is the inherent inaccuracy in the measurement of curve progression. With the Cobb technique, a three-dimensional deformity is measured two-dimensionally. Most studies have used an arbitrary change of 5 degrees to reflect an actual spinal change. However, in a blind study to measure the precision of the Cobb angle by five different orthopedists on the AP projection of 50 roentgenograms, the variation in the measurement was found to be surprisingly high.[84] The average error was 9 degrees (2 standard deviations), with a range of +5 to +15 for individual orthopedists. In another study, Dawson and associates compared radiographs of 60 patients with the radiograph of each patient taken standing and then taken in a special frame a few minutes later.[85] They found a variation in curve measurement from 1 to 23 degrees even with the same physician doing all of the measuring. The significance of this imprecision in measuring is that clinicians must not overreact to every small change between successive radiographs.

What, then, are the factors related to the likelihood of progression during adolescence? This information comes from the follow-up of untreated patients.[37,63,78,83] First, the risk of progression in girls is ten times higher for any given curve measurement than for boys. Second, the size of the curve at presentation is closely related to the risk of progression: the larger the curve when first seen, the greater the risk of progression. Third, the younger the patient at presentation, the greater the risk of progression. The critical time period for rapid progression is puberty. A curve detected before menarche is much more likely to progress (66%) than is one detected after menarche (33%). The Risser sign—a five-stage grading of skeletal maturity based on the appearance of the iliac crest apophysis—is a convenient method of assessing maturation. The lower the Risser sign, the greater the likelihood of progression. And, finally, the curve pattern itself affects the likelihood of progression. Lumbar curves are less likely to increase than thoracic curves.

Lonstein and Carlson have assembled the above factors to create a nomogram for predicting progression in individual cases. Their nomogram uses the formula

$$\frac{\text{Cobb angle} - 3 \times \text{Risser sign}}{\text{chronologic age}}$$

to come up with a "progression factor."[37] Using tables, one can predict that without intervention, a 10-year-old premenarchal girl with a 32-degree curve and a 0 Risser sign would have a greater than 90% chance of a significant curve progression. At the other extreme, a 15-year-old girl who is two years postmenarche with an 18-degree curve and a 4+ Risser sign would have a less than 2% chance of significant progression. Treatment of the second patient by any means is likely to be considered successful if "success" is measured by the lack of curve progression.

The second issue of progression is the increase of deformity after maturity.[31,39,41,42,86] Previously it was taught that the spine was stable after skeletal maturity and progression did not occur. In general, curves of less than 30 degrees at maturity progress negligibly during adulthood. Larger curves progress an average of ½ to 1 degree per year, although not in any regular, predictable way. Thoracic curves between 50 and 75 degrees at maturity are the most likely to progress. The effect of pregnancy on progression in adulthood is totally unpredictable.[33] A few patients have a significant increase in their curvatures during pregnancy, but most have relative "stability" of their curvature. Translatory shifts—lateral subluxation typically of L-2 and L-3—are associated with a greater tendency for progression.[63]

Whereas the effects of gravity and other purely mechanical factors would tend to increase a curve during adulthood, there are many biologic factors that tend to stabilize a curve. The entire spine generally stiffens with aging. In elderly patients, intervertebral spurs or even limited spontaneous ankylosis is not uncommon.

The adverse effect of scoliosis on pulmonary function has long been known.[39,40,43,63,87,88] Only thoracic curves affect pulmonary function by virtue of the curve itself. Generally, only severe thoracic curves—greater than 90 to 100 degrees—significantly affect pulmonary function. These severe thoracic curves, especially if the spine is lordoscoliotic, narrow the AP diameter of the chest. The pattern of pulmonary dysfunction is that of restrictive lung disease and eventually pulmonary hypertension.[61] If scoliosis is severe in early childhood, alveolar development is deficient; total lung and vital capacity are reduced and lung ventilation (measured by the maximal voluntary ventilation) is also reduced.[43,89]

Lung compliance decreases as the chest cage stiffens. When a thoracic deformity is substantial, the oxygen consumption is increased due to the actual increased mechanical

effort of breathing. Bjure and colleagues showed that premature closure of the peripheral airways occurs in the lungs of patients with scoliosis.[87] In their patients, 6 of 133 had airway closures at lung volumes greater than the functional residual capacity (whereas normally this occurs at lower lung volumes).

Muirhead and Corner think that the primary factor in reduced ventilation of patients with scoliosis is diminished lung growth and actual alveolar hypoplasia.[89] Those having the onset of curvature at younger ages (congenital and infantile idiopathic scoliosis) had far more severe diminution in lung volumes and vital capacity. Adolescent patients with idiopathic scoliosis have in general less severe curves and seldom suffered severe decreased vital capacity or total lung capacity. Of their 52 patients with adolescent idiopathic scoliosis with thoracic curves averaging 52 degrees (20 to 93 degrees), only 4 (8%) had moderate to severe diminution of lung volume.[89] Kostuik, in a series of 200 patients with idiopathic curves, also noted the rarity of severe respiratory compromise in adolescent patients with idiopathic scoliosis, even in curves of 100 degrees.[90] He stated that if severe restriction of lung function were found in an adult with severe scoliosis, the likelihood was that the curve was congenital in origin and not idiopathic. In summary, most patients with adolescent idiopathic scoliosis usually have normal lung function. Those with severe curves, an early onset, and lordosis will have varying degrees of a restrictive defect.

The above-mentioned respiratory complications relate to the increased death rate (two times normal rates) in long-term studies of patients with scoliosis. These study populations, however, have included fairly severe deformities and nonidiopathic causes.[31,39,40,88] In the more usual adolescent patients with deformities of less than 100 degrees, the mortality rate does not differ from that in the general population.[63] Shneerson and co-workers studied the cause of death in 38 heterogeneous scoliosis patients in London.[88] Of the deaths, 58% (22) were due to cardiorespiratory failure in patients with a mean age of only 22.3 years. Of the 38 patients, 84% (32) had a vital capacity of less than 1.75 liters, and electrocardiographic evidence of right ventricular hypertrophy was found in 44% of those with curves of 60 degrees to 89 degrees and in 57% of those with curves of greater than 90 degrees. Right ventricular hypertrophy was present in two thirds of those autopsied. Of the 38 deaths, however, 32 occurred in patients with neuromuscular or congenital scoliosis. Therefore, these data should not be extrapolated to apply to the typical adolescent patient with a curve of less than 100 degrees.

Pain due to scoliosis during childhood and adolescence is so rare that its presence should suggest some cause other than adolescent idiopathic scoliosis, such as osteoid osteoma, infection, and the like. On the other hand, backache in the general adult population is so ubiquitous—at least 25% to 50% of the general population, depending on criteria—that it is difficult to prove that scoliosis increases the incidence of back pain. Furthermore, the presence of many patients with severe scoliosis who deny any back pain highlights our poor understanding of the back pain issue. Most long-term studies suggest an incidence of back pain in patients with scoliosis equal to that in the general population.[39,41,86] In patients with severe lumbar curves, however, especially if there is lateral translatory shift, the incidence of back pain does increase. Some authors have found that most patients with pain usually had only mild or moderate but nondisabling discomfort[9,39,63]; others have found an overall increased incidence of disabling pain and that the tendency toward more disabling pain occurs in those patients with more severe curves.[34,36,40] Sciatica is not common. Because back pain is so difficult to objectify and so multifactorial in origin, it may be appropriate to consider scoliosis as only one contributing factor to the etiology of back pain in any individual patient.

The psychological and social effects of scoliosis are real but variable and hard to quantitate. In one of the earliest long-term studies, Collis and Ponseti concluded that there was no significant social dysfunction among scoliotic patients from Iowa.[86] Their patients functioned well as adults and did not appear to suffer increased marital or social problems due to the scoliosis. On follow-up of this same group of 161 patients 14 years later (1983), Weinstein and associates found that 21% (34 patients) actually had a mild psychological reaction to their deformity, such as an unwillingness to wear snug clothing or bathing suits.[41] There was no correlation between the severity of the curve and the psychological reaction. Some patients with severe curves were not at all bothered, while others with mild curves expressed severe psychosocial limitation because of their curves. None required psychiatric treatment, and most patients said that they were more self-conscious during their teenaged and young adult years than they were later. In fact, Ascani and co-workers have shown by follow-up photography that the unpleasant cosmetic appearance tends to become less pronounced with age, even if the radiographic appearance worsens.[31] They also found psychosocial disturbance in their group of Italian patients in 35 of 187 adults (19%), mainly in women with thoracic curves. The same group also had a lower percentage of marriage and only a modest reduction in their ability to do manual labor.

Nilsonne and Lundgren, in a similar long-term study from Sweden, found in a group of 113 adults with moderate to severe scoliosis that 47% of the patients were disabled from work because of the scoliosis and 76% of the women were unmarried.[40] Nachemson, also from Sweden,[39] and Fowles and colleagues from Canada[34] also found similar high rates of disability from work and a lessened likelihood of marriage.

Treatment

The treatment of scoliosis is either operative or nonoperative. Nonoperative treatment has traditionally consisted of observation alone (nontreatment), prescribed exercises, various types of body jackets (orthoses), and, more recently, electrospinal percutaneous stimulation. The vast majority of patients identified early with minor curves (less than 15 to 20 degrees) should be followed with not-too-frequent radiographs—certainly no more than two per year at most—because only 10% will progress to where bracing is necessary. Although there is a natural desire to do "something," there is no proof that prescribed exercises help, even if done on a regular supervised basis.[47,54] Patients with scoliosis under observation should not be restricted from physical activity. Even braced patients may fully participate in physical education and after-school sports. We permit gymnasts, swimmers, and other athletes to remove the orthosis during practice or competition.

The original and most familiar brace system is the Milwaukee brace developed by Blount 40 years ago as a postoperative alternative to a body cast.[48,50,51,56,57,91,92] The Milwaukee brace is properly known as a CTLSO (cervical-

thoracic-lumbar-sacral orthosis). It has a pelvic mold of plastic or leather, anterior and posterior metal uprights, and some type of neck ring or throat mold. Various pads and strap adjustments can be added to push on various areas of the deformity, especially the right rib hump.

The Milwaukee brace achieved widespread acceptance in the 1950s and 1960s and remains today the standard of comparison for nonoperative treatment. Despite its wide usage by the medical community, there have been few long-term prospective studies that document the efficacy in altering the natural history. Many outcome studies have included some patients with curves now known to be nonprogressive, and the studies have not used controls of simultaneous, nontreated groups. The average outcome of treatment in all of the major studies is a curve that some years following the conclusion of treatment is similar to the curve that was present at the onset.[48,51,57]

The strongest evidence for the efficacy of the treatment is the curves that were 30 degrees or greater at the beginning of treatment and that showed a net improvement some years later (albeit this is a minority of cases).[62] The typical response to bracing is characteristic. A child has an initial curve that corrects perhaps 20% to 75% while in the brace. The child wears the brace 23 hours per day for one to five years (ideally until skeletal maturity). At skeletal maturity, the use of the brace is gradually limited to part time. Gradually the curve reverts toward its initial pretreatment measurement. There are many exceptions, with some curves relentlessly progressing and a few patients actually achieving significant correction. However, there are so many variables—type of brace, conscientiousness in wearing it, skeletal maturity—that it is difficult to prospectively predict the outcome in a specific case.

Current indications for braced treatment are in growing children with curves between 30 and 45 degrees or 20 and 30 degrees in whom a documented progression of at least 6 to 7 degrees has occurred. Lesser curves should be observed. Patients with severe thoracic lordosis as well as scoliosis are less suited to braced treatment because of the mechanical disadvantage induced by the severe lordosis.[61] Earlier surgical correction is recommended in these patients.

Various underarm braces have been developed over the past two decades. Their major advantage is that they are hidden by clothing. These are thoracolumbosacral orthoses and they are often known by the city in which they were developed, such as Boston,[93] Miami,[54] Pasadena,[94] and Wilmington.[46] The Boston brace is currently the most widely used and is based on prefabricated modules.[69,93] These braces differ in minor structural aspects, and all work the same way. Progression of the curve can be expected to be arrested in 85% to 90% of patients.

If one reviews the outcomes of series of patients braced with underarm orthoses, there is a preponderance of good results, but many of the patients with success would not be treated today. For example, in the series of Bunnell and colleagues,[46] 41% of patients had curves of less than 20 degrees at the start of treatment. In the Boston series of 401 patients, 106 had curves of less than 20 degrees.[93] After eliminating these 106 lesser curves from analysis, the net results were still satisfactory at follow-up, with 49% unchanged, 39% improved 5 to 15 degrees, and 4% improved greater than 15 degrees. There was a strong correlation between the best correction in the brace (flexibility) and follow-up correction. All patients with curves of more than 50 degrees at the start of treatment progressed and required surgical correction. It is likely that once a curve reaches 50 degrees, biomechanical factors make a brace inadequate in correcting and holding.

Bracing with underarm braces is limited to curves with an apex at T-7 to T-8 or lower. Curves with an apex at T-5 (this is a minority of scoliotic cases) usually require a CTLSO. It is still unclear how many hours per day a brace must be worn. More recent studies have suggested that 16 to 18 hours of brace wear per day may be sufficient.[95] Currently in California, most patients who need bracing are placed in underarm orthoses.

Partly because of the negative psychosocial effects of brace wear,[96-98] especially when prescribed full time, other nonoperative treatment methods have been investigated. Lateral electrical percutaneous muscle stimulation has now been accepted as an effective means of preventing the progression of spinal curvatures.[44,55] The principle is that muscle contraction along the convexity of the curve results in shortening of the convexity. The electricity is delivered through electrode leads wired to a small portable battery-powered pulse generator. Multicenter trials have shown satisfactory control in as many as 85% of cases. Because patients use the device while they sleep—that is, 8 to 12 hours per day—patient acceptance is excellent. Psychological testing has shown significant benefits to night-time electrical stimulation as compared to full-time brace treatment with regards to self-esteem and avoidance of anxiety and depression.[98]

Despite an initial enthusiasm for electrical stimulation, many uncertainties remain. Typical reports have an average follow-up of only two to three years. Despite reports of success with curves of more than 30 degrees, our own experience is not as favorable with curves greater than 35 degrees at the onset of an electrical stimulation: most have progressed and required surgical treatment. The effect of the electrical stimulation on the natural history of scoliosis is still not resolved. Stimulation is accepted better by patients than is external bracing, but further study and follow-up will be required to accurately judge its true efficacy.

Surgical Treatment

Surgical fusion is needed in only a small percentage of the patients with typical adolescent idiopathic scoliosis. Any surgical straightening of a curved spine by instrumentation must be accompanied by a spinal fusion to maintain correction. It is important to realize that metal implants will fail after several years if not accompanied by surgical fusion. Criteria for an operation vary depending on a patient's age, the presence of secondary complications, curve location, cosmetic appearance, willingness to wear a brace, and psychological reaction to the deformity. The presence of the many adult scoliotic patients with untreated moderately severe curves who lead productive, long lives serves to temper any automatic recommendation for surgical treatment based on curve size alone.[49,65,99-101]

Most surgeons would recommend a fusion of the primary curve in adolescents and young adults aged 10 to 20 years with single thoracic curves of more than 50 degrees. The presence of thoracic lordosis lowers the curve magnitude criteria for surgical correction because lordosis makes external bracing ineffective. Usually 40 to 50 degrees is considered a "gray zone" for fusing single curves.[100] Because the risks and complication rate for surgical treatment in adults go up dramati-

cally, the usual preference would be to operate earlier on a younger patient with a lesser curve if it were possible to predict which curves were going to increase significantly during adult life. Certainly, it is much safer overall to operate on a 15-year-old with a 45-degree curve than on the same patient at age 30 with a 65-degree curve.

Controversy surrounds intervening in primary lumbar and double major curves because the risks of pulmonary dysfunction and the cosmetic defect are clearly less than in those with thoracic curves.[63] Nonetheless, in the United States, most surgeons would suggest an operation on adolescents or younger adults with lower curves of more than 50 degrees. There is a general tendency to try to preserve as many intact lumbar motion segments as possible. The rationale for this is the fear that a long fusion ending at L-5, for example, would place unacceptably high stress levels on the single remaining articulation (L5-S1), thus leading to a high incidence of secondary degenerative disc disease and back pain. Cochran and associates, in a review of long-term follow-ups after Harrington rod instrumentation for scoliosis, found an increased incidence of low-back pain related to the level of the distal Harrington hook: 39% at L-3, 62% at L-4, and 82% at L-5 (versus a rate of back pain in controls of 53%).[49] We rarely, if ever, include L-5 as the lowest vertebra in a fusion and generally try to avoid L-4.

The indications for surgical treatment in skeletally mature patients are much less clear.[89] More important than the actual degree of scoliosis are the rate of progression during adulthood, the presence of pain, and cardiopulmonary compromise. Furthermore, the degree of correction in adults is less, and the risk of each complication greater—at least 50% of adults have one or more complications.[34] Therefore, surgical correction of adult scoliosis is usually only done after increased curvature is found during adulthood or prolonged conservative means of relieving back pain fail.

Spinal fusions for scoliosis have been done since 1914.[102] Until the 1950s fusions were done without internal fixation. This necessitated prolonged casting and recumbency, often of three to six months. In the past 30 years, several systems of internal fixation (spinal instrumentation) have been developed. The Harrington rod is still the most widely used device and the one against which all others must be compared.[99] The fusion and hardware may either be anterior between the vertebral bodies (Dwyer, Zielke) or posterior between the laminae (Harrington, Wisconsin, Luque, Cotrel-Dubousset) (see Figure 2). Each system has its enthusiastic supporters and its own particular risks. Each implanted rod system is only an adjunct to the main purpose of surgical correction—a solid arthrodesis.

Anterior procedures give greater correction and allow shorter fusions because discs are removed and the spine is loosened. Anterior procedures are most useful in thoracolumbar and lumbar curves. Anterior instrumentation, however, does not function well in the mid or upper thoracic spine where the vertebral bodies are smaller. Anterior hardware entails additional, potentially catastrophic, risks (although rare) because of the proximity of the great vessels, lymphatics, and ureters.

For most patients with moderate curves (40 to 90 degrees), a single posterior fusion with internal fixation is most appropriate.[60,99,100] In adolescents, a correction of 50% of the curve is typical. The actual correction depends more on the inherent flexibility of the spine than on the type of hardware. The newer systems of hardware, such as Cotrel-Dubousset, Wisconsin, and Luque, offer more fixation points on the spine and thus often eliminate the need for postoperative casting or

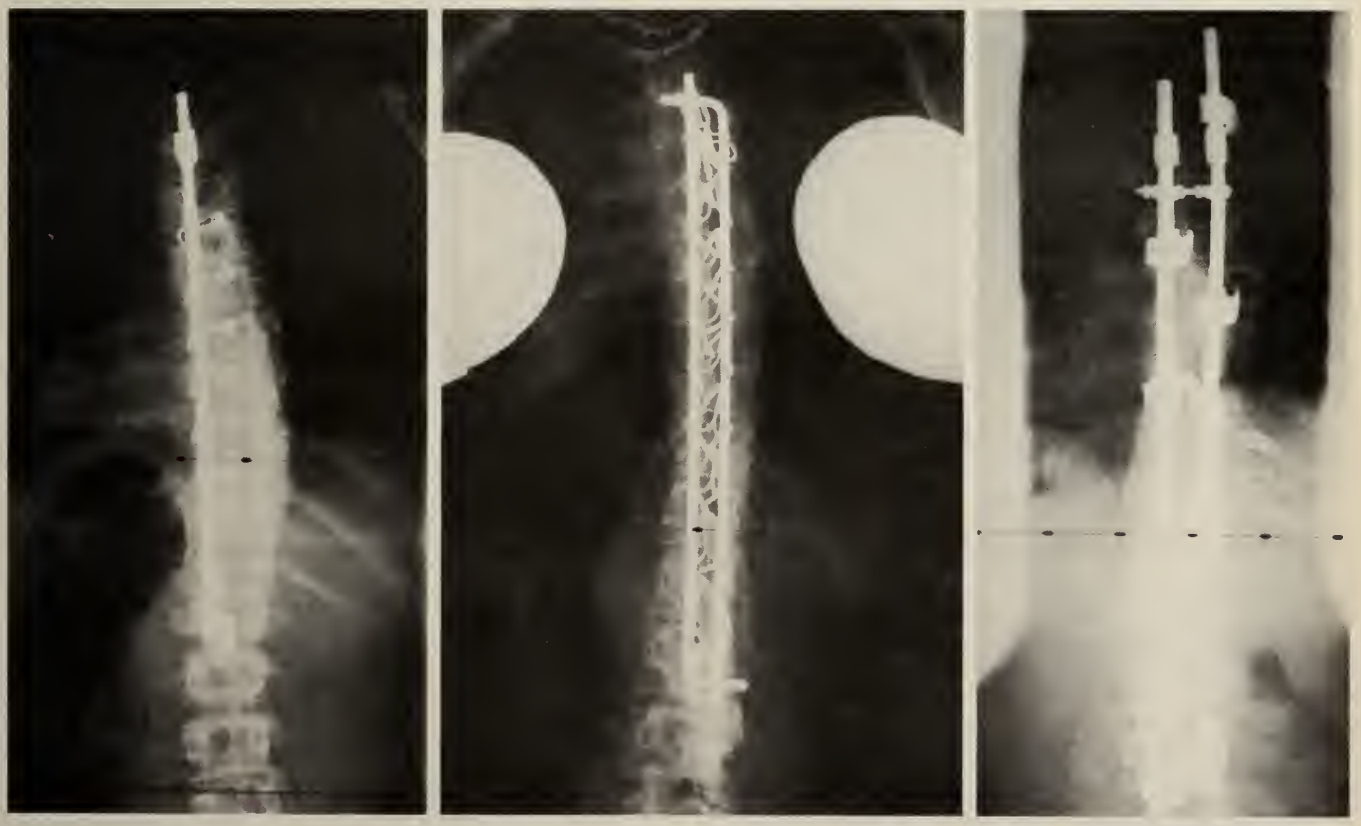

Figure 2.—The photoradiographs show postoperative correction following posterior fusion and spinal instrumentation with **(left)** Harrington rod, **(middle)** Luque rod, and **(right)** Cotrel-Dubousset rod.

bracing.[60] In adults, the correction averages somewhat less. For more severe, intrinsically rigid curves, a two-stage procedure is commonly done. An anterior transthoracic, retroperitoneal exposure of the spine accomplishes disc removal over four to seven levels and "loosens" the spine. One to two weeks later, the second stage is a posterior spinal instrumentation with fusion.

Spinal fusion for scoliosis is a major undertaking with potentially serious risks. Neurologic catastrophes have occurred, such as acute paraplegia and nerve root loss.[101] This is more common following spinal instrumentation and particularly if attempts are made to achieve excessive correction of the curve. In a survey study conducted in 1975, MacEwen and co-workers found an incidence of neurologic complication of 0.75%.[53] This included all different types of scoliosis, including rigid congenital curves. The incidence of neurologic complication in idiopathic scoliosis is probably much less. Nonetheless, to lessen this risk, most spinal surgeons use intraoperative neurologic monitoring or a wake-up test at the completion of the instrumentation and before skin closure.[101]

Summary

School screening has greatly extended our knowledge of the epidemiology and natural history of scoliosis. The goals of accuracy and cost-effectiveness of screening must be continually reassessed, however.

Currently the most favored theories of etiology and pathogenesis involve subtle neurologic dysfunction, perhaps in a patient with a genetic predisposition to scoliosis. Other intriguing theories involve contractile protein abnormalities and calcium imbalance. Most probably, scoliosis is not a single disease entity but is a final common outcome from a number of causes.

Pulmonary dysfunction, increased mortality, back pain, and psychological problems are complications of severe scoliosis. The correlation of these factors with the severity of the spinal deformity varies. Clinicians must be familiar with the likelihood of the above problems so that needless anguish and treatment can be avoided while continuing to emphasize appropriate treatment for those who truly need it. Spinal bracing has become much more cosmetically acceptable using underarm braces. Bracing or electrospinal stimulation is effective for some patients, but many patients with intrinsically nonprogressive curves have been unnecessarily treated in the past. We still have no accurate way to prospectively identify those whose curves will progress from those who remain unchanged. Surgical spinal fusion remains the mainstay of operative treatment. The goal of surgical correction is to obtain a balanced spine with a solid fusion.

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The Clinical Significance of Water Pollution

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs Homer A. Boushey, Professor of Medicine, and David G. Warnock, Associate Professor of Medicine, under the direction of Dr Lloyd H. Smith, Jr, Professor of Medicine and Associate Dean in the School of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, School of Medicine, San Francisco, CA 94143.

RICHARD K. ROOT, MD*: *The possible clinical consequences of water pollution are of increasing concern to the public and to the medical community. We are fortunate to have Joseph LaDou, MD, at this conference to discuss this important topic. Dr LaDou has had long experience in the field of occupational medicine and is currently Acting Chief of the Division of Occupational and Environmental Medicine.*

JOSEPH LADOU, MD†: Under the most favorable conditions, water undergoes a constantly repeated cycle of purification through evaporation, cloud formation, rainfall, collection in unpolluted waterways, and again followed by evaporation. In heavily populated and industrialized areas and in agricultural areas, the recycling for purification is not capable of dealing with the widespread entrance of pollutants into the environment. The resulting contamination of water leads to various health effects that are of growing concern to public health agencies throughout the world.

Since the industrial revolution and particularly since World War II, the environment has become increasingly contaminated. The impact of industrialization has been a slow, steady increase in air contamination and water pollution through the improper disposal of manufacturing wastes and unusable by-products. The problem since World War II has been the proliferation of many new chemicals whose health effects in most cases are neither understood nor studied.

The National Research Council of the National Academy of Sciences concluded from a recent study that toxicologists have relatively complete information on health hazards for only 10% of pesticides and only 18% of drugs in use today.[1] Moreover, at least a third of pesticides and drugs have never been tested for toxicity. The problem with generally used commercial chemicals is even more serious because nearly 80% of these chemicals have never been tested and little is known about those that have been studied.

This situation, together with a growing incidence of storage tank leaks, accidental spills, the improper disposal of wastes, and the breakdown of sewage and water distribution systems, has created growing public and governmental concern about just how contaminated our drinking water is, the health effects that can be expected, and the means of ameliorating the problem.

Industrialized nations face proliferating problems of water contamination as new materials, products, and processes continue their rapid growth. Third world countries will increasingly be faced with the problem as their industrialization proceeds. The United States alone has a very serious and growing problem because its industries produce greater than a quarter of a billion tons of hazardous wastes annually, and it is expected that the amount will double by the end of the century. We Americans are the highest per capita waste producers in the world. Moreover, there are more than half a million hazardous waste dump sites—as well as polluted pits, ponds, and lagoons covering thousands of acres—that are contributing to a frightening decrease in potable water (Figure 1).

Water samples from 16.8% of systems serving fewer than 10,000 people and 28% of those supplying a greater number have been found to contain at least one volatile organic substance. Nor are the rural areas free of the problem because of the abundant use of pesticides and herbicides for which new formulations are being developed continually as insects and plants become immune to the destructive effects of current products.

Health Effects of Water Contamination

A growing number of reproductive toxins and carcinogens are appearing in the nation's drinking water. Also present are a number of other hazardous substances that may be injurious to human health. Both the Environmental Protection Agency (EPA) and the public have become increasingly concerned because drinking water from either surface or groundwater sources often contains substances that are hazardous to health. To date, the levels of contamination have been generally low, although the levels appear to be rising as more and more contaminants gain access to our waterways and particularly our groundwater supplies.

Waterborne disease has increased in recent years, probably because of overloading of treatment plants with source water of poor quality. As a consequence, many rivers used for potable water at present contain at least 10% sewage effluent. Worldwide, it is estimated that 100 million people are drinking water that contains substantial amounts of sewage effluent. The efficiency of water treatment plants designed to reduce the numbers of bacteria, viruses, and protozoa in drinking water is diminished by the increasing levels of organic chemicals contaminating the input water being treated. Thus, the increasing rates of water poisonings may actually

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reflect the more serious problem of environmental contamination with many thousands of organic chemicals, metals, and mining fibers.

At this point, more is suspected about the health effects of contaminated water than is known. Can contaminated water result in cancer, reproductive diseases, and other health effects in addition to those known to occur from the presence of infectious agents?

Individual cases are seldom helpful in studying the problems of environmental pollution. Public health agencies rely on epidemiologic studies to evaluate clusters of illnesses and possible health effects on populations from known episodes of contamination of the environment. Epidemiologists have attempted to determine the potential for health risks from water containing toxic substances. Their efforts have resulted in an extensive literature that is largely based on the assumption that groundwater is unpolluted and, therefore, that populations drinking from aquifers could be used as controls in studying populations drinking surface waters. These studies also made little or no attempt to adjust for other variables, such as diet. The epidemiologists were unable to determine a correlation between drinking water and cancer rates and reproductive outcomes because the urban populations studied drank primarily chlorinated surface waters while the rural populations drank waters from aquifers that were usually unchlorinated. Eventually, the equivocal findings of repeated studies were finally called into question, and it was found that groundwater was also contaminated with toxic substances and in concentrations similar to those found in surface waters. No attempt should have been made to interpret data until groundwater quality had been thoroughly evaluated. A further complication occurs because the deeper the aquifer, the greater the possibility for contamination from naturally occurring radioactive materials and heavy metals.

Many investigators have reviewed the entire epidemiologic literature in this area and have concluded that it is almost impossible to arrive at any reliable clinical conclusions about the health hazards of drinking contaminated water.[2] In no other area of health research have the limitations of epidemiology been so amply demonstrated as has occurred in attempting to quantify the health hazards of contaminated drinking water.

Sources of Water Contamination

There are three primary sources of environmental contamination affecting the quality of drinking water: improper waste management of synthetic hazardous substances, the injudicious use of pesticides and herbicides by both agriculture and home users, and deterioration of water system conduits. These affect both surface and groundwater. The contamination of surface water has been addressed by both state and federal authorities, and efforts have met with some success. The problem of contaminated groundwater is a more difficult issue to resolve because the source is seldom easy to locate and because the contamination may have continued for long periods before the location is sufficiently identified to take countermeasures.

Groundwater used for drinking purposes and agricultural use is taken from water contained in geologic formations called aquifers, which may be quite close to the earth's surface or far below. This water is one of our most important natural resources. It provides about 50% of the nation's drinking water in urban areas and 90% in rural areas. This water, 30 trillion gallons of which are pumped to the surface each year, is also vital to agricultural irrigation.

The primary contributors to water contamination are chemical production and use, mining and smelting, petroleum operations, and agriculture. As rainwater and melting snow filter down to replenish the aquifers, they can carry with them toxic wastes that contaminate the water. Contamination thus occurs when pesticides and herbicides are applied, toxic waste tanks leak residues of chemical and petroleum wastes, wastes are improperly disposed of in landfills, and toxic substances are inadvertently spilled. Unfortunately, many toxic chemicals and other wastes are not dissipated by microorganisms in the soil or filtered out during their passage to the aquifers.[3]

The most long-lived and dangerous wastes are the biorefractory chlorinated hydrocarbons, including trichloroethylene, tetrachloroethylene, and carbon tetrachloride, which are heavily used in some industries. As they filter down, they are trapped in the aquifers and remain there.

The filtering-down process may be slow or rapid, depending on the nature of the surmounting soil (Figure 2). The movement is faster through unconsolidated sand or gravel and slower where the surmounting structure is consolidated rock. Consequently, aquifers that are surmounted by unconsolidated material are at greater risk from contamination. The rate of flow may range from a fraction of an inch to several feet a day.

The degree and health effects of toxicity that the aquifer water will attain depend on the volume of the substance filtered down and thus its concentration in the aquifer, the life span of the substance, and the length of time it is ingested. Although some claim that only a small proportion of the nation's aquifers are contaminated, the extent of such contamination is probably much higher because a preponderance of groundwater sources has never been tested. In California, for example, 25% of public wells using groundwater have been found contaminated by organic chemicals.

Landfills

The dumping of toxic wastes in landfills, which has been a common practice, is a prime source of groundwater contamination. The EPA has estimated that 75,000 industrial landfills and 15,000 municipal landfills exist throughout the nation. Although 30,000 of them are thought to be abandoned, these sites can still be leaching poisons into the groundwater

Figure 1.—Americans are the highest per capita waste producers in the world, each citizen adding more than a ton of new hazardous waste to the environment each year.

system. Many companies dispose of their toxic wastes in company-owned closed sites, and it is thought that these sites have accounted for the disposal over time of more than 200 billion pounds of industrial wastes. Thus, both abandoned and active disposal sites are very likely contributing heavily to aquifer contamination.[4]

In the area of landfills, improper waste management and rain and snow leaching down through the soil constitute a very serious problem. The EPA acted on this situation by establishing a date in late 1985 by when all toxic landfill operators must attest that they were effectively monitoring the purity of neighboring groundwater and have assets or insurance to cover environmental damages. If they could not meet these requirements, they were in danger of being closed down. This move caused some environmentalists to hope that the EPA would be successful in controlling groundwater contamination. The reality is that the EPA is so ill-informed and inspects sites so infrequently that most dumping sites continue to operate and continue to threaten the integrity of our underground water resources.

Surface Impoundments

Pits, ponds, or lagoons that are used to store, treat, or dispose of industrial wastes are dangerous sources of groundwater contamination. It is estimated that at least 170,000 of these sites exist in the nation and that 90% of them are unmonitored. Of these surface impoundments, 70% are unlined, thus allowing seepage through the soil; 30% are unlined and located directly above groundwater sources; and 10% not only are unlined, but also are located within a mile of drinking-water wells (Figure 3). These data, however, reflect sites that are state-permitted impoundments for which considerable information is available. Because those not approved by the states are not included, the extent of this hazard could very likely be much more threatening.

Figure 2.—Identification of chemicals contaminating the soil after removal of leaking drums is necessary to detect the highest priority cleanup sites.

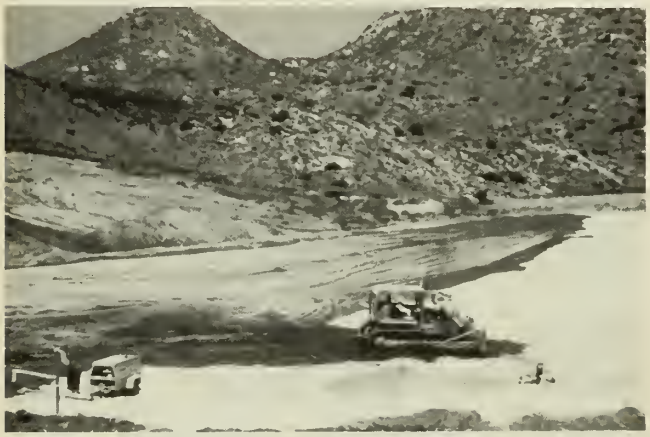

Figure 3.—Public indignation over the presence of hazardous waste landfills is resulting in a faster closure rate than new facilities are approved. In California, we are left with only one Class 1 site able to accept delivery of liquid wastes.

Underground Storage Tanks

At least 3.5 million underground storage tanks exist throughout the United States for storing petroleum products, chemicals, and toxic wastes such as solvents. Such tanks can leak because of material fatigue, improper location, or any of a number of other factors. Obviously, leaking of these tanks presents a serious hazard to groundwater sources and can cause severe contamination. In California, for example, a 6,000-gallon fiberglass storage tank leaked 58,000 gallons of solvent over a period of 18 months, resulting in the contamination of three aquifers and a number of wells providing drinking water for a large community. Even smaller leaks—as little as half a gallon a day—have seriously contaminated drinking water supplies.

Despite the seriousness of the problem, however, only a third of the states have enacted legislation to protect surface and groundwater. Legislation in those states usually requires a permit for installing a tank, inventory controls by the owner, tank testing and monitoring, and the use of leak detection equipment. There are also regulations governing the closing down of tanks.

Because the EPA estimates that 10% of underground storage tanks are leaking, it is possible that there are at least 300,000 sources of groundwater contamination from such tanks. Unfortunately, the total could be much higher because few states have initiated widespread testing.

Asbestos Contamination of Water

In 1973, large amounts of amphibole asbestos fibers were discovered in Lake Superior, a source of municipal water supplies. This discovery aroused both state and federal concern. Sources of asbestos fibers in drinking water include erosion in asbestos-containing natural elements, pollution caused by logging and construction, and the deterioration of asbestos-cement pipes used for transmitting the water.

Asbestos contamination of drinking water is not uncommon, as indicated by available data. Most Americans consume asbestos fibers in their drinking water, ranging from usually less than 1 million fibers per liter to more than 1 billion fibers per liter, depending on where they are located. When drinking water flows through areas of natural asbestos, however, the amount of fibers can be higher than 10 billion fibers per liter.

But water is not the only source of ingested asbestos fibers. Recently it was determined that asbestos fibers are also contained in a number of foods, particularly processed foods, and other ingestible products. The items found to contain these fibers include aspirin tablets, chewing gum, mayonnaise, lard, catsup, sticky rice, and many other foods. These products have been found to contribute at least a million fibers a day to the average American diet. The effect on the outcome of epidemiologic studies will be very limiting because there is no readily available technique for determining the asbestos

fiber content of various foods. Moreover, previous studies that have not proved a correlation between asbestos in drinking water and gastrointestinal and genitourinary cancers are seriously flawed because they were unable to take fiber-containing foods into account.[5]

Effectiveness of Conventional Water Treatment Processes

Many water treatment plants have been shown to provide a drinking water at the tap that is more heavily contaminated with organic chemicals than is the input water to the treatment process. It appears that the more water is treated, the more contaminants are dissolved by the water from machines, conduits, and the general environment.

Adding chlorine to drinking water is an effective treatment for reducing the likelihood of waterborne infections. Chlorine treatment—and various other chemical disinfection processes—creates chemical contamination of drinking water. First, chlorination increases the amount of chloroform in the water, raising chloroform content from a few micrograms per liter to several hundred. It also produces chlorinated hydrocarbons and chlorinated ring compounds in the water or enhances those that are already present so that they may become more toxic or carcinogenic than they were before treatment.[6]

The primary exposure of humans does not result from drinking the water. Much more chloroform is absorbed in steamy showers and hot baths through the respiratory tract than is consumed in a few liters of daily water intake.

A major market of water treatment systems has emerged in recent years. Charcoal filtering systems for home use are not only common sources of waterborne infection, they have failed to show any significant long-term benefits, whether used as small filters attached to faucets or as major appliances built into the plumbing of kitchens and bathrooms. One study showed that deionizing charcoal filtering of drinking water in the home reduced the concentration of chloroform and benzene, but water treated by this method was found to contain higher concentrations of tetrachloroethylene, methyl methacrylate, and styrene than are found in unfiltered tapwater.

Finally, bottled water apparently does not offer a satisfactory alternative to chlorination or filtering. Commercially bottled artesian water has been found to contain acetaldehyde, benzene, bromodichloromethane, dichloropropane, diethylether, ethylacetate, and toluene, not to mention the growing concern that artesian waters may be contaminated with radioactive materials and heavy metals. The State of California published a document—the most requested state publication in recent years—outlining some of the problems with the simplistic hope that by paying more money for drinking water that is delivered in bottles to the home, citizens could protect their health by not drinking tapwater. In most instances, bottled water provides no essential advantages over tapwater, and it fails to protect citizens from exposure to volatile organics inhaled during showering and bathing.[7]

Most of the information we read about water purity is derived from gas chromatography-mass spectrometry. This expensive analysis is capable of identifying less than 10% of the organic content of drinking water. Most of the heavier molecules contributing to the mutagenic and carcinogenic activity of drinking water must be measured by liquid chromatography-mass spectrometry, analyses much too expensive for most public agencies to afford. When water purity is alleged to consumers, the data are invariably derived from gas chromatography-mass spectrometry.

Water Softening

Water softening, which is often used in areas of particularly hard water, has been studied for its effect on the health of water drinkers. Because the method used replaces calcium in water with sodium, it presents a possibility of increased fatalities from sudden cardiac events and may contribute to the development of hypertension. The data to support either of these possibilities are easily dismissed. Many studies have failed to show an elevated risk of heart disease and death from sudden cardiac events with the drinking of soft water. Although some studies have implicated water with high levels of sodium with hypertension in the water drinkers, the sodium is only a small portion of the dietary sodium provided by food in these poorly controlled studies. Few conclusions can be made from available research.[8] It is important to remember, however, that a patient on a low-sodium diet should also be warned to ascertain the sodium level in the drinking water, which in these circumstances may reflect the major portion of daily sodium intake.

QUESTIONS AND ANSWERS

F. Jay Murray, PhD*: *Would you comment on the reasons behind private industry's slowness to develop and use newer treatment technologies for hazardous waste disposal?*

Dr LaDou: There are two basic reasons why private industry continues to use the low-cost landfilling practices approved by the EPA. Government has failed to create the incentives for private industry to develop new treatment technologies and to put them into use after they become available. There are no tax incentives or other examples of government efforts to deal realistically with the hazardous waste problem in this country. Second, the use of incineration is moving slowly in all areas of the country because each community says "not in my backyard." There are many more examples of local governments denying approval and permitting of new incinerators than there are installations each year.

Wallace Epstein, MD†: *Santa Clara County has more EPA "Superfund" cleanup sites than any other county in the US. What is the quality of water in the Silicon Valley?*

Dr LaDou: The much-publicized water contamination from leaking underground chemical storage tanks has not affected the major sources of drinking water in Santa Clara County. The water there is, however, interesting to consider because its seasonal variation in quality reflects the reality of many areas of the country. During the winter and spring when abundant rainwater naturally fills the aquifers that provide the bulk of the county's drinking water, water quality is very high. During the late summer and fall months, when the aquifers are unable to provide sufficient water for the community demands, they are recharged with reservoir water and with water of the poorest quality in the area, the delta water from San Francisco Bay. These seasonal variations are entirely separate from the trivial levels of water contamination that have resulted from the chemical storage tank problems of the local industry (Tables 1 and 2).

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TABLE 1.—*Level of Contamination of Santa Clara County Tapwater*

Content	*Parts/million*
Trihalomethanes	1.5 to 85.0
Filterable residue	89.0 to 622.0
pH	7.6 to 9.2

MARVIN H. SLEISENGER, MD*: *Is pesticide regulation improving the quality of our water?*

DR LADOU: Pesticide regulation in this country helps to protect our drinking water from contamination, but does not adequately protect us from pesticide contamination of water or food. There is about two times the level of residual pesticide in imported foods than exists in domestic crops. We banned the use of DDT in this country in the mid-1970s, yet its manufacture worldwide exceeds 100,000 tons per year.

Pesticide regulation is but one of many examples of the need for international regulation and cooperation in the handling of materials that gain entrance into the environment and into our food and water.

*Professor and Vice-Chair, Department of Medicine, and Chair, Medical Service, Veterans Administration Medical Center, San Francisco.

TABLE 2.—*Inorganic Compounds in Santa Clara County Tapwater*

Inorganic Compound	*Level, mg/liter*	
Calcium	7.7 to 38.4	
Chloride	4.5 to 110	(250)*
Copper	<0.04 to 1.08	(1.0)
Fluoride	<0.1 to 1.5	(1.0)
Iron	<0.04 to 0.33	(0.30)
Magnesium	2.3 to 17.3	
Nitrate	<1.0 to 16.4	(45)
Potassium	<0.5 to 4.0	
Sodium	4.5 to 143	
Sulfate	5.4 to 143	(250)
Zinc	<0.02 to 0.45	(5.0)

*Numbers in parentheses refer to recommended United States drinking water standards (from EPA[9]).

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Epitomes

Important Advances in Clinical Medicine

Preventive Medicine and Public Health

The Scientific Board of the California Medical Association presents the following inventory of items of progress in preventive medicine and public health. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome, and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, research workers or scholars to stay abreast of these items of progress in preventive medicine and public health that have recently achieved a substantial degree of authoritative acceptance, whether in their own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Preventive Medicine and Public Health of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to Division of Scientific and Educational Activities,
California Medical Association, PO Box 7690, San Francisco, CA 94120-7690

Cholesterol Reduction—Pros and Cons

More than 5 million Americans have symptomatic coronary artery disease, and, though age-adjusted mortality due to this condition has declined steadily since the 1960s, it remains the leading cause of death in the United States. Thus, clinicians' efforts to prevent the onset or progression of coronary disease can provide major benefits.

Controversy has existed regarding the importance of elevated cholesterol as a risk factor and the impact of reduction efforts. Recent studies, however, have confirmed the significance of the risk and shown the benefits produced by reducing elevated levels.

In October 1987, the National Heart, Lung, and Blood Institute recommended that baseline cholesterol levels be determined for all persons aged 20 years or older. Persons with values below 200 mg per dl should be retested every five years. Those with confirmed values of 200 to 239 mg per dl who do not have other risk factors or evidence of coronary artery disease should be placed on a low-fat diet and retested annually. Risk factors to be considered, in addition to the major ones of smoking and hypertension, are male sex, diabetes mellitus, cerebrovascular or peripheral vascular disease, weight greater than 30% above standard, high-density-lipoprotein cholesterol (HDL-C) levels of less than 35 mg per dl, and a family history of premature coronary artery disease. Those in the 200 to 239 mg per dl range with evidence of heart disease or two or more risk factors and those with confirmed values above 239 mg per dl should have a lipoprotein analysis. If analysis reveals low-density-lipoprotein cholesterol levels of 130 mg per dl or greater, specific diet therapy and follow-up are recommended. Details of this program have recently been published in the *Archives of Internal Medicine.*

Given the most recent information available, it appears that all major modifiable risk factors, including elevated cholesterol levels, should be addressed. Patients with confirmed total cholesterol levels above the 200 to 220 mg per dl level or low HDL-C levels (less than 35 to 40 mg per dl) are candidates for therapy to prevent premature coronary artery disease. Higher cholesterol levels, or the presence of multiple risk factors, increase the urgency for intervention. Diet, weight control, and exercise may be sufficient to lower cholesterol levels while simultaneously increasing HDL-C levels. If these efforts fail, however, drug therapy should be considered.

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Penicillinase-Producing *Neisseria gonorrhoeae*

Penicillinase-producing *Neisseria gonorrhoeae* (PPNG) organisms were first isolated in 1976, although gradually increasing resistance on a chromosomal basis was noted 30 years before, shortly after the introduction of penicillin treatment for gonorrhea. For the past ten years, worldwide surveillance of resistance patterns has caused alarm, as both plasmid-induced (PPNG) and chromosomally mediated resistance in *N gonorrhoeae* have appeared and crossed borders from one country to another.

In 1986, PPNG was reported to infect 16,600 patients in the United States, representing only 1.8% of all *N gonorrhoeae* infections. Chromosomally mediated resistance to antibiotics other than penicillin remains a smaller proportion still. Although these numbers are small, there is concern that outbreaks would be difficult to control, and worldwide experience lends credence to that fear. In the Far East, PPNG accounts for as much as 50% of all organisms isolated and, as a consequence, spectinomycin was adopted by the US military as the drug of choice for treating gonorrhea.

Susceptibility testing by the Centers for Disease Control of *N gonorrhoeae* organisms from around the US has shown resistance to spectinomycin, tetracycline, trimethoprim-sulfamethoxazole, cefoxitin, and erythromycin.

Epidemics of PPNG or other antibiotic-resistant organisms tend to appear in hyperendemic areas, such as New York City and Los Angeles. Outbreaks have occurred elsewhere, however, in both homosexual and heterosexual groups.

There is evidence that some antibiotic resistance patterns develop because of antibiotic use, but they may also be plasmid related. Several laboratories are doing susceptibility testing of *N gonorrhoeae* routinely. Physicians treating gonorrhea must maintain a high level of suspicion and concern about treatment failures and think of resistance of the gonococcus rather than poor compliance as a cause.

Physicians should maintain an awareness of local resistance patterns and question their patients about both domestic and international travel. The days of a shot of penicillin and a pat on the back to treat gonorrhea are clearly over, and vigilance on the part of physicians may help prevent epidemics of resistant organisms in the United States.

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Preventing Transmission of Human Immunodeficiency Virus Infection

In June 1986, the US Public Health Service held a workshop on the acquired immunodeficiency syndrome (AIDS) at Coolfont, Berkeley Springs, West Virginia, in which the course of the AIDS epidemic was projected through 1991. Some of the most important estimates were as follows:

- By the end of 1991, there will have been a cumulative total of more than 270,000 cases of AIDS in the United States (up from more than 38,000 as of July 1986), with more than 74,000 cases occurring in 1991 alone.
- By the end of 1991, there will have been a cumulative total of more than 179,000 deaths from AIDS in the US, with 54,000 of these occurring in 1991 alone.
- The vast majority of AIDS cases will continue to come from the currently recognized high-risk groups, including homosexual men and intravenous-drug users.
- New AIDS cases in men and women acquired through heterosexual intercourse will increase from 1,100 in 1986 to almost 7,000 in 1991.

Although one drug, zidovudine, has resulted in several months' prolongation of life and fewer opportunistic infections in AIDS patients, there is no satisfactory treatment for the causative agent of AIDS, the human immunodeficiency virus (HIV). Prospects for an effective vaccine against HIV are not promising for at least five years and possibly until the turn of the century. Therefore, for the foreseeable future, the most effective way of reducing the spread of HIV infection is through educating the public about the transmission of HIV, especially those persons at a higher risk for AIDS. Physicians have an important role and responsibility to play in this educational campaign in their daily interactions with patients.

The educational message must be direct rather than vague. "Always use a condom with a spermicidal lubricant from the start of sexual intercourse until the finish" is preferable to "Avoid bodily secretions." Educators, including physicians, must be prepared to use the vernacular and to take into account cultural traditions and practices of diverse groups, including ethnic minorities and homosexual men. Preventing AIDS among intravenous-drug users may be challenging because of the distrust of authority in this population, and their sexual partners may be difficult to reach because the partners do not necessarily have contact with drug treatment centers. Nevertheless, drug users should be encouraged to use methadone and other treatment programs.

The voluntary, confidential use of the HIV antibody test should be encouraged for those who may be at risk for infection, both to identify persons in low-risk groups for education in preventing further transmission, and to serve as a starting point in identifying persons who may benefit from treatment as effective antiviral and immunomodulating agents become available. Patients should be counseled adequately about the implications of a confirmed positive HIV antibody test both before and after the test and should be assured of strict confidentiality. The final decision about whether to take the HIV antibody test should be made by the patient.

As HIV infection becomes more prevalent, the risk that health care workers will be exposed to blood from infected patients also increases, especially when blood precautions are not followed. The Centers for Disease Control have issued guidelines for preventing HIV transmission in health care settings. These guidelines emphasize the need for health care workers to treat blood and body fluids from *all* patients as potentially infected with HIV and to adhere rigorously to infection control precautions for minimizing the risk of exposure to blood and body fluids of all patients.

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Preventing Influenza in Older Adults

The US Public Health Service's Advisory Committee on Immunization Practices recommends annual influenza immunization for persons aged 65 years and older and for other high-risk groups. Until recently, the recommendation was based primarily on extrapolated efficacy data from younger populations, rather than on direct studies in older age groups. Recent research not only confirms the efficacy of flu shots in older age groups, but suggests that the benefits of immunization may be greater than generally appreciated.

From data from the National Hospital Discharge Survey, it has been calculated that persons age 65+ have 370 per 100,000 excess hospital admissions during an influenza epidemic. This rate is more than ten times that of younger adults. The national cost of these excess hospitalizations was estimated at $185 million. Yet, in a study of noninstitutionalized older adults in a large health maintenance organization, flu shots prevented 72% of influenza- and pneumonia-related hospital admissions during epidemic years.

In older adults in long-term-care facilities, vaccine efficacy is less (about 30%) due to age- and disease-related im-

pairments in immune function. But flu shots are considerably more effective at preventing the complications of influenza. Studies of a large series in long-term-care facilities report vaccine efficacies of 47% to 95% in preventing hospital admission, pneumonia, and death.

Present national vaccination rates of 20% are far below the national goal of 80%. Vaccination reminders mailed in the fall to high-risk persons have been shown in several settings to increase vaccination rates to 45% to 60% in the first year of mailing. Vaccination rates of 60% to 70% appear possible with yearly, repetitive reminders. Health care providers should strongly consider mailing flu-shot reminders to their high-risk patients when flu shots become available each fall.

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Smoking Control—Policy and Legal Methods

As a consensus has emerged that exposure to secondhand smoke is harmful, many smoking control advocates have shifted their attention from encouraging smokers to quit to restricting smoking in workplaces and public places. The rationale underlying this shift is the belief that smoking restrictions will not only protect the health of nonsmokers but also will encourage smokers to cut down or quit. This latter outcome could result from both a subtle increase in the social pressure against smoking and a limiting of the time available to smoke. There is evidence that smoking restrictions do encourage smokers to quit smoking. When Pacific Northwest Bell banned smoking in the workplace, enrollment in smoking cessation programs went from 13 to 174 employees per month.

The tobacco industry views the nonsmokers' rights movement as a major threat, and it has waged an aggressive campaign against the enactment of smoking restrictions. This tactic achieved some initial success as the tobacco industry used multimillion dollar advertising campaigns to defeat small, independent nonsmokers' rights groups in Florida and California. However, as the nonsmokers' rights groups shifted their attention from statewide campaigns, in which large advertising budgets are critical, to city and county campaigns, in which grass-roots support is critical, the tobacco industry suffered a series of defeats. The attention from and the success of local smoking restrictions in turn led to the enactment of state restrictions. Currently 10 states and more than 260 cities and counties have enacted laws restricting smoking in public places.

Experience with smoking restriction in both workplaces and communities shows that they are generally easy to implement and enforce. When Pacific Northwest Bell banned smoking, there were no lawsuits because of the ban, the unions supported the ban, and none of the 15,000 employees quit work because of the ban. In San Francisco, the ordinance against smoking in the workplace, which is one of the oldest and toughest, has not caused any lawsuits, and no employer has been fined for noncompliance.

The nonsmokers' rights movement could be one of the most effective forces against smoking, and health care professionals should encourage the enactment of smoking restrictions whenever possible.

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Preventing Dependency in the Elderly

Dependency is usually measured in terms of functional measures such as activities of daily living, which includes competencies in feeding, bathing, dressing, toileting, ambulation, and continence. According to a 1982 national survey of long-term care, 19% of the 65-and-over age group had some degree of limitation in their activities of daily living, and 4% of the population was severely disabled. This proportion rises dramatically in the old-old age group—that is, 85 years of age and older. In fact, men and women age 85 years and older are four times more likely to be disabled than those aged 65 to 74. Almost half, or about 46%, of persons 85 years and older are disabled compared with only about 13% of persons age 64 to 74.

Another measure of dependency is nursing home admissions. Data from the 1985 National Nursing Home Survey indicate slightly less than 5% of the population age 65 years and older reside in nursing homes. This percentage rises dramatically for the older age subgroups, with 10% of persons older than 75 years of age and more than 22% of persons 85 years of age and older living in nursing homes.

The leading chronic conditions causing limitation of activity and loss of independence for the elderly, according to a 1982 survey by the National Center for Health Statistics, were arthritis, hypertension, hearing impairment, heart conditions, orthopedic impairment, sinusitis, visual impairment, diabetes mellitus, varicose veins, and arteriosclerosis. Arthritis and rheumatism, although the leading chronic conditions in the elderly, account for relatively few deaths and only 2% of hospital days. They do, however, account for 16% of all days spent in bed.

One important new concept that has developed in looking at the relationship between mortality and disability has been the calculation of "active life expectancy." Using the longitudinal data of all the persons in Framingham, Katz and colleagues computed the active life expectancy, which they defined as the expected number of years of remaining life in which one remains independent (needs no help in performing activities of daily living). For example, independent persons between the ages of 65 and 69 years had an "active life expectancy" of 10.0 years but a total life expectancy of 16.5 years. Therefore, an average of 6.5 years were lived in a state of functional dependency. A major goal, then, of preventing dependency in the elderly would be to extend the "active life expectancy"—that is, adding life to years and not just years to life. This is perhaps a better statistic to monitor the health of the elderly than just mortality rates or life expectancy tables.

Results of recent studies suggest that, in the absence of

chronic diseases that impose limitations on activities, older persons do not have to have a substantial reduction in physical fitness with aging. Many cases of physical decline with aging are simply a matter of deconditioning. Furthermore, 65% of elderly persons living in the community describe their own health as excellent, very good, or good compared with others their age. Several measures can be taken to prevent dependency in the elderly, and the elderly should be targeted for preventive programs. Although some studies have questioned the influence of good health practices on health status and disability in the elderly, recent studies have affirmed the value of basic health practices for the elderly. The findings suggest that important health practices for elderly persons are refraining from smoking (ever or currently), maintaining weight control, engaging in some form of physical activity such as walking or gardening, getting seven to eight hours of sleep a night, and maintaining social networks. More attention also needs to be given to a significant measure of a loss of independence—nursing home placement. Some possible modifiable risk factors for nursing home admissions include functional impairment in activities of daily living, household isolation, a lack of social support, falls, and cognitive impairment. Finally, iatrogenic illnesses contribute to a lot of disability in the elderly and are probably the most preventable diseases in old age. The most common types are inappropriate medications, nosocomial infections, and the overuse of therapeutically imposed bed rest.

Because there are many factors in preventing disability in the elderly that go beyond the traditional disease-specific preventive approach, a multifunctional geriatric assessment is crucial in evaluating the elderly to determine what are the important problems and also to develop the necessary intervention plan to keep the elderly functioning as independently as possible in the community for as long as possible.

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Chemical Contamination of Fish as an Emerging Environmental Health Concern

In California and other states, concern about the contamination of fish by organic and inorganic chemicals is increasing. In the past three years, the California Department of Health Services has evaluated various fish and game contamination situations and issued health advisories for persons consuming fish taken from certain locations where elevated levels of chemical contaminants are found in fish. The chemicals involved include methylmercury, selenium, DDT, and polychlorinated biphenyls (PCBs). Exposure to some of these chemical substances in the regular daily diet of the general population in this country is unavoidable because virtually all fish have some body burden of the above substances. While clinical illness is not certain to result from eating fish at the higher levels of contamination found, increased regular ingestion could increase the health risk. The health advisories are consumption guidelines incorporating a safety factor, and they specifically consider the greater sensitivity of population subgroups such as pregnant women and young children. They are also specific for certain species of fish found in certain locations. The purpose of these guidelines is to minimize excessive exposure to environmental contaminants.

Some of the specific locations in California for which advisories have been issued are as follows: the Grassland area in Merced County; Harbor Park Lake in Los Angeles County; Lake Nacimiento in San Luis Obispo County; the San Francisco Bay delta region; Clear Lake in Lake County; Salton Sea in Imperial and Riverside counties; southern California, including Santa Monica Bay, Palos Verdes Peninsula, and the Los Angeles-Long Beach Harbor area; Lake Berryessa in Napa County; and Lake Herman in Solano County.

Methylmercury affects the nervous system, with paresthesia as the earliest symptom of poisoning, and it can harm a fetus. Poisoning episodes have resulted from the ingestion of methylmercury-contaminated fish in Japan and contaminated bread in Iraq. A minimal level of clinical effect has been established at 200 ng mercury per ml blood. Selenium at high intake levels can produce gastrointestinal disturbances, a loss of hair and nails, skin lesions, nervous system effects, and, based on animal data, may cause adverse reproductive and developmental effects. Human toxicity has resulted in the United States from overdosing with a selenium supplement containing a dose level many times above that indicated on the label and in China from ingesting contaminated food crops where selenium from stoney coal reached the soil and was taken up by the plants. Selenium intoxication from fish consumption has not been documented. The primary health concern relating to DDT and PCBs is the potential carcinogenic risk. Low birth weights and smaller head circumferences have been observed in newborn infants whose mothers consumed moderate quantities of PCB-contaminated fish from Lake Michigan.

Persons who sport fish should be informed of the health advisories that are published in the state sport fishing regulations obtainable where fishing licenses are sold or by contacting local health officials. Clinicians should also be aware of early clinical manifestations associated with high exposure to these chemical substances and the biologic monitoring methods used for detecting these substances for confirming exposure.

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Ozone Air Pollution

Ozone is a reactive oxidizing gas formed in ambient air by the action of sunlight on automobile exhaust and some industrial emissions. Although control measures undertaken since the passage of the Clean Air Act in 1970 have considerably decreased ozone concentrations to which people are exposed, more than 60 urban areas violate the federal hourly standard of 0.12 ppm. The Los Angeles basin, for example, exceeded

this level on 148 days in 1986. Failure to meet this health-based standard has potential clinical implications, as summarized below.

The effects of acute exposure to ambient ozone include cough, chest tightness, substernal pain on inspiration, dyspnea, and a decreased ability to perform sustained exercise. Spirometric tests of people exposed in controlled laboratory settings show a significantly increased airway resistance and bronchial hyperreactivity and decreased forced expiratory volumes at concentrations as low as 0.12 ppm. Persons at risk from acute exposure to such low levels of ozone include adults and children involved in vigorous outdoor activity, such as heavy manual labor, jogging, or cycling. Physical exertion per se is not considered to enhance susceptibility to the effects of a given dose of ozone; rather, increased ventilation augments the effective dose delivered to the lungs. People at rest or doing light exercise, however, do not generally have respiratory symptoms or significant changes in lung function until ozone concentrations approach 0.3 ppm. Although epidemiologic studies indicate that even low concentrations may provoke asthmatic attacks, controlled exposure studies suggest that persons with preexisting pulmonary disease are not remarkably more sensitive to ozone's bronchoconstrictive effects than healthy people.

Children appear to experience pulmonary function decrements of a similar magnitude to those seen in adults, yet do not report increased respiratory symptoms to the same extent, suggesting that they may be less aware of somatic warnings to curtail exposure. This is of interest because stage 1 smog alerts, in which schools are advised to restrict outdoor activities, go into effect when ambient ozone concentrations reach 0.2 ppm, even though symptoms and signs of toxicity are observable in exercising persons at lower concentrations. Furthermore, decrements in lung function have been reported to persist for several days after exposure to ambient ozone concentrations less than 0.2 ppm.

One of the principal uncertainties about ozone's toxicity is the relationship between repeated exposures and chronic respiratory disease. Animal studies suggest that chronic exposure to ozone concentrations occurring in typical urban air can result in centriacinar inflammation and small airway structural changes. Recent epidemiologic evidence suggests the existence of significant associations of photochemical oxidant exposure with an accelerated decline in lung function and with symptoms of chronic respiratory disease; however, this issue has not been adequately explored.

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Editorials

Death and Dying—A Public or Private Matter?

ELSEWHERE IN THIS ISSUE a medical student wrestles with the principles promoted by The Hemlock Society, which advocates positive euthanasia at the hands of physicians, albeit in compliance with the understood desire of a terminally ill patient and all others who may properly be concerned. This raises many important issues, none of which is likely to go away soon. For the first time, and to the extent it ever occurred at all, what was a very personal and intimate matter between doctor and patient is now becoming one of public concern and is sure to generate public debate.

Physicians are revulsed by the idea of contributing purposely or willingly to the death of a patient. Yet, we all know that compassion may lead to an understanding with a patient and family, particularly within the framework of a close and long-standing doctor-patient relationship, that will in one way or another hasten the death of a suffering and terminally ill patient for whom there is no hope. The acts have more often been ones of omission rather than commission, although not always, as with a decision to terminate life support systems. There is a fine line between a decision such as this and active euthanasia administered by a physician, but it is a line that physicians are reluctant to cross and have not crossed.

The scene and the drama are now beginning to shift into the public arena. There are a growing number of persons who are appalled by the suffering of many patients who are terminally ill when it is within the power of their physicians or of society to end this apparently needless suffering, much as a veterinarian might end the suffering of a beloved family pet when its life expectancy is short and its quality of life irreversibly gone. Often, these persons are driven by their own first-hand experience with long, expensive, and—to them—unnecessarily prolonged suffering in a member of their family. This has profoundly affected many people and has led to such things as living wills, durable powers of attorney, and now, The Hemlock Society.

More crass social, economic, and even political considerations are beginning to touch upon the scene and the drama of death and dying. It is now virtually routine to try to revive a dying person of any age or with any fatal illness by attempting cardiopulmonary resuscitation, if nothing else. This is accepted, even expected, by present day society. In many cultures, including our own, there is some special reverence for the elderly, but how much reverence will or should there be when it comes to allocating increasingly expensive and scarce resources to perpetuating the lives of those whose productivity and quality of life are gone, and who do not wish to live any longer regardless of the cost to them or to others, especially when it is also a fact that vast numbers of younger Americans who have their full lives ahead of them do not have sufficient resources available for the health care they need? So far, the voting power of the elderly has been an important political factor in determining this distribution of national health care resources. And then, there is the harsher impact of health care economics. For better or worse, the "bottom line" is beginning to dominate more and more of the health care in this nation. It is well known, and worth noting, that Medicare data show that most of the major health care costs are incurred in the last year or so of life. One may ask, and some already have, how cost effective is much of this terminal care, and what is being achieved at what expense? Again, from a crass economic standpoint, a sudden death is least costly and, therefore, most cost effective, since little or no health care is needed. Next most cost effective would seem to be a shorter terminal illness and a comfortable and pain-free death for a fatally ill patient with very little for which to live. In all of this one can easily foresee the spectre of social, economic, political, and even family pressures on the ill and the elderly to "voluntarily" seek active euthanasia if this were ever to receive widespread social acceptance.

It remains to be seen whether we are ready to accept the view of The Hemlock Society. If and when an initiative appears on the California ballot—and there is reason to believe that one may soon qualify—there will then be a test of public opinion. In any case, and whatever the outcome, death and dying are becoming much less private and much more public matters. Physicians cannot help but be deeply concerned. The issues that are raised strike at the heart and soul of what medicine is all about.

MSMW

The Treatment of Scoliosis

THE ARTICLE "Adolescent Idiopathic Scoliosis" by Rinsky and Gamble elsewhere in this issue is thorough, well documented, balanced, and informative. It is about a disorder of great concern to parents, pediatricians, and orthopedists. At the outset the authors correctly state that the diagnosis of scoliosis is straightforward and is made on clinical and radiographic examination. The epidemiology has been explained using data provided from school screening programs. The precise etiology evades us, although there are some tantalizing experimental and clinical phenomena that point to one cause or another. However, it is in the area of nonoperative and, to a lesser extent, operative treatment that significant clinical controversy exists.

A general historical survey of the evolution of the treatment of adolescent idiopathic scoliosis may help focus the current dilemma that many treating orthopedists face. Prior to the late 1940s, there was no reasonable nonoperative means of preventing progression of a scoliosis curve. Prolonged casting and bed rest were infrequently employed. Patients and parents were advised that surgical correction was a last and dangerous resort. Nobody understood the natural history of the disorder. The patient whose curve unpredictably increased was advised that some day a surgical procedure would become absolutely necessary and the risk, at that future date, acceptable.

In the 1950s and 1960s, the Milwaukee, Pasadena, and other braces were used with considerable success to prevent progression of the curve. Surgical treatment was still plagued with complications and was performed only in centers by a relatively few expert spinal surgeons. Reliable natural history data remained unavailable. Only moderate and large curves were being treated.

In the 1970s, in response to the patients' cosmetic and functional objections to the Milwaukee brace, orthopedist–orthotist teams developed many varieties of underarm braces. Almost simultaneously, the widespread adoption of school

screening for the early detection of small curves produced a very large pool of patients to be treated. Although they still did not know the cause, orthopedists thought they could now use braces to keep small curves small, thus avoiding surgical intervention. At the same time, alternative spinal instrumentation techniques were introduced. These promised more correction and better fixation than the standard Harrington rod procedure.

By the early 1980s orthopedists were comfortable with their techniques of managing patients with idiopathic scoliosis. They could prevent progression of the curve that had been detected by screening. When treating patients with severe scoliosis that had escaped the screening net, they had reliable and relatively safe surgical ways of correcting the scoliosis. However, natural history studies done in countries where nonoperative treatment of idiopathic scoliosis was not so uniformly implemented shed some doubt on the probability of progression of small curves. These were precisely the curves that the screening programs were designed to detect. Furthermore, retrospective studies showed that teenagers and young adults in the United States and the United Kingdom were not wearing the braces prescribed to the extent or in the way advised by their orthopedist. When criteria developed for prospective analysis of a new method of nonoperative treatment of scoliosis (surface electrical stimulation) were applied to the bracing programs, success rates were much lower than expected.

During this frustrating period with nonoperative care in the early and mid-1980s, controlled hypotensive anesthesia, spinal cord monitoring, autologous blood collection, and improved surgical techniques combined to make the surgical treatment of scoliosis shorter, safer, and more predictable than ever before. However, when the natural history of curve behavior was compared with the time-consuming supervision of a questionably successful nonoperative treatment program with either a brace or electrical stimulation, it led many orthopedists into fatalistic analyses of their nonsurgical roles. Their pessimism about the success of nonoperative methods influenced their patients' decisions on whether or not to have surgical correction and fusion.

The Scoliosis Research Society is sponsoring an international prospective study on the results of bracing, electrical stimulation, and the absence of treatment on the progression of idiopathic scoliosis. The patients included in the study fit strict criteria and their curves would generally be expected to increase to some extent without treatment. It is hoped that the results of this and other analyses will provide us with the natural history of this disorder and the effect our current treatments have upon it.

It will be five to ten years before reliable long-term data are available from this project. Meanwhile, despite the fact that nonoperative treatments are less successful than we should like, we still have the obligation to pursue them in those patients in whom we have reason to expect substantial curve progression for whatever reason. Even though early surgical results have improved, the preliminary data on the long-term effect of spinal fusions on adjacent lumbar discs suggest increased rates of degeneration. Until statistically valid final conclusions are available, more enthusiastic support by patients' orthopedists for existing nonoperative treatment methods would definitely increase their effectiveness.

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Cigarette Smoking Is Bad Practice

It was nearly 50 years ago that Alton Ochsner first called attention to an association between cigarette smoking and cancer of the lung. It has been more than 20 years (1964) since the Surgeon General of the United States first proclaimed that smoking was injurious to health. Since then, even though Koch's postulates have yet to be fulfilled, epidemiologic data have accumulated that leave no doubt that avoidance of smoke and smoking should be high on the agendas of personal and public health care. Smoking has now been associated not only with cancer in the oral cavity, esophagus, larynx, and lung, but with diseases of the cardiovascular system and other organs, as well. Clearly, there is something toxic to humans in tobacco smoke, and clearly, smoking, particularly cigarette smoking, is a bad practice.

At first, physicians were slow to face up to this harsh reality. For a while, it was "Do as I say and not as I do," as the physician puffed away on a cigarette. This, however, has changed. Within the medical profession there has now developed a groundswell of disapproval of smoking. It is being banned at medical meetings, and people are being asked not to smoke in physicians' offices or in hospitals. The message is getting out into society. Restaurants are beginning to have no smoking areas, hotels to have smoke-free rooms, and there is real progress to prohibit smoking in the workplace.

All of this is well and good. But is it enough that the medical profession clearly disapproves of smoking for good medical reasons and supports professional and public policies that deter smoking or tend to make it socially unacceptable or at least embarrassing to the smoker? Perhaps not. It has been established that patients do listen to their physicians, and there is reason to believe that much more can be done in the way of physician counselling of patients to help them stop smoking. Many physicians may need to learn new skills to do this well, but there is a growing body of data and experience that can help. Cigarette smoking is not only in itself a bad practice, but it can also be good practice for physicians to actively encourage their patients to quit and then find ways to help them to do it.

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Case Reports

Spontaneous Gas Gangrene at a Site of Remote Injury—Localization Due to Circulating Antitoxin

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In 1967 an American soldier suffered shrapnel injuries to both hands and both legs. Gas gangrene developed bilaterally in the lower extremities, necessitating disarticulation of both hips. In 1984, following a nonpenetrating injury to the hand, gas gangrene caused by *Clostridium perfringens* developed in his left hand. The infection was atypical because it remained localized and was associated with abundant polymorphonuclear leukocytes (PMNs) at the site. We showed that a neutralizing antibody directed against θ-toxin—a known leukocytolysin—was present at the time of diagnosis and increased fourfold subsequently. We speculate that this antibody prevented θ-toxin-induced PMN destruction at the site, resulting in their accumulation and the location of gas gangrene.

Report of a Case

The patient, a 38-year-old Vietnam veteran, presented to the Veterans Administration Medical Center at Boise, Idaho, because of fever and chills for two days and a painful, swollen left hand.

His medical history was significant for gas gangrene that developed during April 1967 in Vietnam following a land mine explosion. The patient suffered shrapnel injuries to his upper and lower extremities and his abdomen. Gangrene of both legs ultimately developed, requiring disarticulation at both hips. He also suffered bilateral amputation of the small fingers at the metacarpophalangeal joints and amputation of the right index finger distal to the interphalangeal joint due to shrapnel injury.

Additional medical problems included diabetes mellitus with episodes of ketoacidosis, duodenal ulcer disease, hypertension, persistent purulent drainage from his left hip, and recurrent *Staphylococcus aureus* abscesses over the posterior aspect of both shoulders. There was a history of intravenous drug abuse in the remote past.

Four days before admission, the patient became inebriated and fell off a bar stool, breaking the fall by landing on his hands. The next morning, the left hand was painful, though there was no evidence of penetration, bruising, or abrasions. He said he had not had a previous infection in that area but did recall seeing a pimple over the left index finger about two weeks before the event.

On physical examination he appeared alert, was confined to a wheelchair, and complained of pain in the left hand. His temperature was 37.8°C (100°F), pulse was 100 beats per minute, respirations 16 per minute, and blood pressure 130/86 mm of mercury. The lungs were clear to auscultation and percussion. Examination of the heart revealed a normal sinus rhythm without murmur or rub. The abdominal examination disclosed numerous old surgical scars and disarticulation of both hips.

The patient had the hand deformities and amputations as described above. The left thumb-index web was considerably swollen and tender to palpation. Crepitus was noted over the metacarpophalangeal joint dorsally. Neither lymphangitis nor proximal extension of infection beyond the hand was apparent.

Roentgenograms of the left hand showed gas in the soft tissues overlying the dorsal metacarpophalangeal joint and the first web space. Numerous small, metallic-like objects, presumably shrapnel, were present in the soft tissue (Figure 1).

Laboratory studies elicited the following values: leukocyte count 11,600 per μl with a differential count of 72% segmented neutrophils, 5% bands, 15% lymphocytes, and 8% monocytes. The hematocrit value was 47.1%, platelet count 379,000 per μl, and the sedimentation rate was 52 mm per hour. The prothrombin and partial thromboplastin times were within normal limits. Serum chemical levels were normal with the exception of the serum glucose value, which was 267 mg per dl.

A regimen of aqueous penicillin G, 2 million units given intravenously every four hours, cephalothin sodium, 1 gram every six hours, and gentamicin sulfate, 80 mg every six hours, was begun. On surgical exploration, necrotizing fasciitis was apparent, with grey discoloration of the muscles and a bubbly, clear grey fluid exuding from the entire first dorsal interosseous and volar thenar adductor compartments. Ne-

Figure 1.—A roentgenogram of the left hand shows gas in the soft tissue **(arrow)**. Note the shrapnel fragments acquired 17 years previously.

(Stevens DL, Laposky LL, McDonald P, et al: Spontaneous gas gangrene at a site of remote injury—Localization due to circulating antitoxin. West J Med 1988 Feb; 148:204-205)

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crotic fat and fascia were debrided, and the wound was left open to ensure proper drainage. Gram's stain of the surgical specimens revealed many large, gram-positive bacilli and abundant PMNs. No other bacteria were seen. Anaerobic cultures yielded a pure culture of *C perfringens,* and aerobic cultures were negative. The administration of cephalothin and gentamicin was discontinued after the first dose. Penicillin therapy was continued for 14 days, the wound healed, and the patient was discharged. A follow-up examination showed complete resolution of the infection, and no recurrence of infection at that site was apparent over the ensuing six months.

Discussion

Gas gangrene caused by clostridial species occurs most commonly following extensive trauma (sufficient to impair blood supply) or abdominal surgery. In this setting, other bacteria such as *S aureus, Streptococcus pyogenes* or *Escherichia coli,* and the like may be present with *C perfringens, Clostridium septicum,* or *Clostridium novyi* at the site of infection.[1] This patient's clinical course of gas gangrene was atypical in three ways. First, the infection was likely related to activation of latent bacilli or spores. We hypothesize that recent blunt trauma to the hand resulted in a suitable anaerobic environment conducive to the growth of latent organisms acquired 17 years earlier. Such "spontaneous" cases of gas gangrene are rare; only 14 cases have been reported in the English-language literature.[2-4] In addition, most of these cases occurred as a result of metastatic spread of spores or bacilli from a distant portal of entry rather than activation of latent forms at the site of a prior trauma. Second, this gas gangrenous infection was atypical in that it was localized without rapid spreading, and, third, abundant PMNs were present at the site of infection.[5-7] More than 60 years ago, military surgeons noted that purulent drainage was not present in areas of clostridial gas gangrene and that histologically such areas contained degenerating muscle bundles, numerous bacteria, and a paucity of acute inflammatory cells.[8] The conspicuous absence of PMN infiltration into gas gangrene lesions raised the possibility that *C perfringens* exotoxins might be leukocytolytic.[8]

That θ-toxin is indeed a potent leukocytolysin is suggested by studies done by Wilkinson and Allan[9] and by us[10] that showed that human PMNs incubated with θ-toxin underwent distinct morphologic changes, showed decreased viability, and lost chemotactic responsiveness.

Explanations for the abundance of PMNs at the site of infection in our patient include the following: the *C perfringens* strain did not produce θ-toxin, or immunity to θ-toxin may have been acquired during his first episode of gas gangrene 17 years previously. To investigate the former possibility, θ-toxin production was assayed using sheep blood agar plates.[7] Zones of hemolysis due to the presence of θ-toxin were similar to those produced by a reference strain of *C perfringens* (American type culture collection strain #13124). To investigate the presence of antitoxin in the patient's serum, toxin-neutralizing studies were done using both Ouchterlony double diffusion in wells punched into sheep blood agar plates and by the neutralization of θ-toxin-induced hemolysis of 1% suspensions of sheep erythrocytes. Results showed that at the time of admission the patient's serum contained neutralizing antibody sufficient to inactivate 4 hemolytic units of purified θ-toxin per milliliter of serum. In addition, a serum specimen obtained 28 days later showed antibody sufficient to neutralize 16 hemolytic units of θ-toxin per milliliter of serum.

This patient was unique in several ways:

- He had two separate episodes of gas gangrene in his lifetime;
- The second episode of gas gangrene developed in a site remote from the first episode and was likely due to spores that had been dormant for 17 years;
- The infection was localized (in this instance to a discrete portion of the hand);
- Systemic manifestations of gas gangrene were not present;
- Abundant PMNs were present at the site of infection;
- Antibody against the potent leukocytolysin, θ-toxin, was present at the time of diagnosis and increased in titer during convalescence.

We speculate that PMNs in nonimmune patients are destroyed at the site of gas gangrene by θ-toxin, but that in our patient, circulating antitoxin neutralized θ-toxin at the site of infection, resulting in PMN accumulation and localization of infection. Thus, a preexisting antibody against θ-toxin did not prevent infection but may in part have attenuated the manifestations of gas gangrene.

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Primary Hepatocellular Carcinoma Following Perinatal Transmission of Hepatitis B

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PRIMARY HEPATOCELLULAR CARCINOMA is one of the most commonly occurring cancers in Asia and Africa. In these areas, most cases of this cancer are associated with chronic hepatitis B infection. It is assumed that exposure to the hepa-

(Tong MJ, Govindarajan S: Primary hepatocellular carcinoma following perinatal transmission of hepatitis B. West J Med 1988 Feb; 148:205-208)

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ABBREVIATIONS USED IN TEXT

AFP = α-fetoprotein
ALT = alanine aminotransferase
anti-HAV = hepatitis A virus antibody
AST = aspartate aminotransferase
HBeAg = hepatitis B "e" antigen
HBIG = hepatitis B immune globulin
HBsAg = hepatitis B surface antigen
HBV = hepatitis B virus

titis virus occurs at an early age and leads to a lifelong viral carrier state. In Asia, perinatal transmission of hepatitis B accounts for as many as 50% of the lifelong carriers, the remainder of whom are infected during their preschool years. After a yet-unknown period of chronic hepatitis B infection, there is integration of the hepatitis B virus (HBV) DNA into hepatocytes and, in some patients, primary hepatocellular cancer will develop by the fourth or fifth decade of life. In Taiwan, this cancer accounts for 20% of all cancers occurring in the adult population, and almost all cases have associated HBV markers.[1,2] A prospective study showed that adult carriers positive for the hepatitis B surface antigen (HBsAg) have a 223-times greater risk for the development of primary liver cancer when compared with HBsAg-negative persons.[3]

Although uncommon, primary hepatocellular carcinoma has been detected during childhood. The following is a case report of an Asian male child born in the United States who acquired HBV infection via perinatal transmission from his HBsAg-positive carrier mother and primary liver cancer developed when he was 5 years old.

Report of a Case

Mother

The patient, a para 1, gravida 1, 27-year-old woman, was born in Thailand and immigrated to the United States in 1975. There was no previous history of jaundice, blood transfusions, illicit drug use, or contacts with other persons with hepatitis in either the patient or her husband. After an uncomplicated pregnancy, she was delivered of a full-term male infant in August 1980. Two months later, a blood screen revealed a serum aspartate aminotransferase (AST) level of 330 IU per liter and a bilirubin of 1.2 mg per dl. The patient tested positive for HBsAg, positive for the hepatitis A virus antibody (anti-HAV), and negative for immunoglobulin M anti-HAV. The husband was negative for HBsAg. The physical examination revealed only a palpable liver edge. Follow-up laboratory tests elicited the following values: serum alanine aminotransferase (ALT) 89 IU per liter, hepatitis B "e" antigen (HBeAg) positive, and serum HBV DNA 50 pg per 0.5 ml. In February 1982, a liver biopsy showed findings consistent with chronic persistent hepatitis B. Since then, liver test values have been normal. In September 1984, she converted to anti-HBe positivity and the serum HBV DNA became undetectable. At present, she is asymptomatic and has remained HBsAg-positive.

Child

The patient, a male infant, was the full-term product of an uncomplicated pregnancy. Because of the findings from his mother's blood tests, the patient was tested at 2 months of age and found to be HBsAg-positive. His serum AST level was 35 IU per liter (Figure 1). During the ensuing months, the AST level rose to a high of 1,055 IU per liter, and he was positive for HBeAg. At this time, a physical examination revealed neither jaundice nor organomegaly. In October 1981, the serum AST level was 305 and ALT 213 IU per liter. In January 1982, both his liver and spleen were enlarged. In June 1983, a liver biopsy specimen showed fragmented pieces of liver with fibrous expansion into the portal areas (Figure 2). There was moderate mononuclear infiltration that extended into the periportal parenchyma. Also, areas of irregular regeneration and lymphocyte cuffing of the hepatocytes were noted. There were occasional "ground glass" cells. The findings were consistent with chronic active hepatitis, type B, with fibrosis approaching cirrhosis. In January 1984, he was positive for the hepatitis Be antibody. In April 1985, on a follow-up visit, he was noted to be asymptomatic and growing normally. On physical examination he again had an enlarged liver and spleen.

In January 1986, he had anorexia, vomiting, and experienced frequent nosebleeds. His abdomen was noted to be enlarging, and he had right upper quadrant pain. At this time, physical examination showed palmar erythema and a firm,

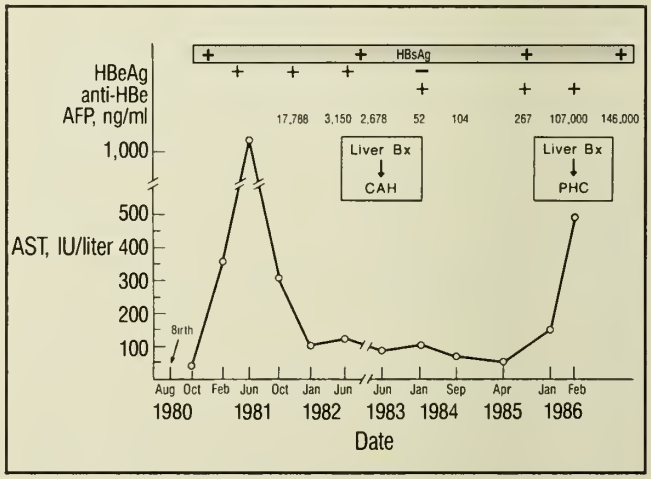

Figure 1.—The serologic and biochemical course of a 5-year-old boy, hepatitis B surface antigen (HBsAg)-positive, with primary hepatocellular carcinoma. AFP = α-fetoprotein, AST = aspartate aminotransferase, anti-HBe = hepatitis B "e" antibody, Bx = biopsy, CAH = chronic active hepatitis, HBeAg = hepatitis B "e" antigen, PHC = primary hepatocellular carcinoma

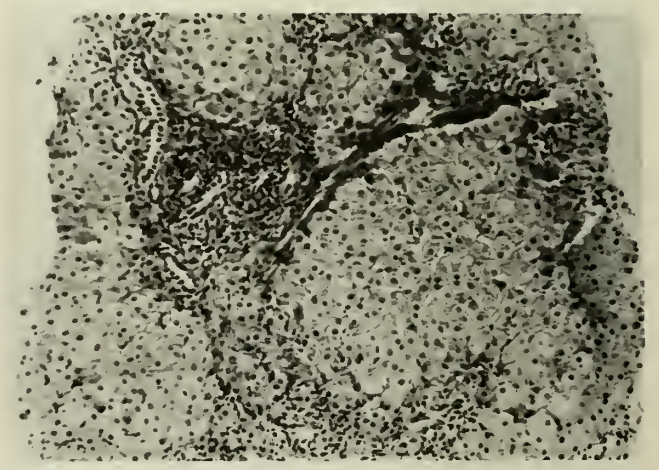

Figure 2.—The liver biopsy taken when the patient was 3 years of age showed fragmented pieces of liver with fibrous expansion into the portal areas. Mononuclear infiltration extending into the periportal parenchyma was noted along with irregular regeneration and lymphocyte cuffing of the hepatocytes. These findings are consistent with chronic active hepatitis and early cirrhosis (hematoxylin and eosin, original magnification × 60).

TABLE 1.—*Characteristics of Pediatric Cases With Tissue Diagnosis of HBsAg-Positive Primary Hepatocellular Carcinoma*

Study	Patients, No.	Sex	Age, Years	Ethnic Origin	Family Members HBsAg-Positive	Comments
Shimoda et al, 1980[8]	1	M	6	Japanese	No	Exchange transfusion at birth
Chang et al, 1984[9]	4	M	4,7,9,7	Chinese	Yes	2 brothers from 2 families
Heyward et al, 1985[10]	3	M	8,10,11	Alaskan Eskimo	Yes	Detected by elevated α-fetoprotein levels
Tanaka et al, 1986[11]	1	M	4	Japanese	Yes	HBV-DNA integration in tumor tissue
Wu et al, 1987[12]	20	12M/8F	8 mo to 15 yr	Chinese	Yes	Chronic active hepatitis and cirrhosis in 33% of cases
This report	1	M	5	Thai	Yes	Perinatal transmission of hepatitis B virus

HBsAg=hepatitis B surface antigen, HBV=hepatitis B virus

enlarged liver that was about 12 cm below the right costal margin. In addition, a tender mass was palpated below the epigastrium. Laboratory tests showed a serum AST level of 147 IU per liter, ALT 487 IU per liter, bilirubin 2.5 mg per dl, alkaline phosphatase 521 IU per liter, and the α-fetoprotein (AFP) level was 146,000 ng per ml. An ultrasound examination and computed tomography of the liver showed a large lesion of the right lobe. A liver biopsy specimen showed the presence of a well-differentiated, trabecular type of hepatocellular carcinoma (Figure 3). The liver not involved with tumor showed scattered parenchymal inflammation and numerous ground-glass cells. The patient died in September 1986.

Discussion

Primary hepatocellular carcinoma usually occurs between the fourth and fifth decades of life and is uncommon during the childhood years. The case presented herein is one of the first reported of a child acquiring HBV infection via the perinatal route that rapidly progressed to chronic active hepatitis B and tissue-documented primary hepatocellular carcinoma when he was 5 years old. In this age group, a definitive diagnosis of the type of liver tumor requires tissue confirmation because hepatoblastoma is a common malignant disorder occurring during childhood, which is also associated with increased α-fetoprotein levels.[4] Therefore, microscopic examination of tumor tissue is necessary to distinguish between primary hepatocellular carcinoma and hepatoblastoma.

In this patient, the serum AFP levels of greater than 100,000 ng per ml at the time of the diagnosis of cancer were similar to levels detected in adult patients with hepatic carcinoma. α-Fetoprotein is an α_1-globulin that is normally synthesized by fetal hepatocytes and reaches its peak production at 13 weeks of gestational age.[5,6] Serum levels then gradually decline and, in most infants, serum levels of AFP are usually low or undetectable at birth. Transient elevations in an infant may be noted with acute liver disease during the neonatal period, but persistent elevations seldom occur except in cases of hepatoblastoma, teratoblastoma, and ataxic telangiectasia. In the case presented herein, retrospective analysis of a specimen of our patient's serum showed extraordinarily high values of AFP at 14 months of age. At this time, there was no evidence of diseases other than chronic hepatitis B. The levels of AFP detected at 14 to 22 months of age were also much higher than those noted with chronic liver disease, and in the absence of other conditions causing the increased AFP levels, one may speculate that this patient was harboring primary hepatocellular carcinoma by 14 months of age. In adult patients with the cancer, fluctuating levels of AFP have been noted, and in two persons, initially elevated AFP levels fell to within the normal range even in the presence of increasing tumor sizes.[7]

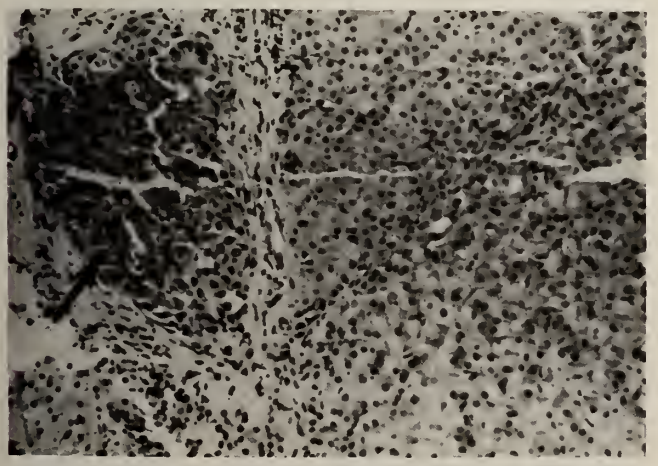

Figure 3.—The liver biopsy specimen taken when the patient was 5 years of age showed a well-differentiated, trabecular type of primary hepatocellular carcinoma **(arrow)** (hematoxylin and eosin, original magnification × 60).

There have been five recent reports describing primary hepatocellular carcinoma in the pediatric age group.[8-12] All of the cases were male, and many of their family members were HBsAg-positive (Table 1). One report of integration of HBV DNA into the tumor tissue in a 4-year-old boy suggested that in the childhood cases of the cancer, the HBV may have exerted its oncogenic properties after a short incubation period.[11] Also, other genetic or environmental influences may play a role in the development of primary hepatic carcinoma because it developed in two young brothers in two separate families.[9] Although chronic active hepatitis B and early cirrhosis were present in the case reported here, less than 35% of patients in the pediatric age group had advanced liver disease.[12] This finding suggested that contrary to the case in adults, childhood cases of primary hepatocellular carcinoma may arise in a setting independent of the development of cirrhosis, and, in this instance, the HBV may play a major role in oncogenesis.

At present, it is clear that the perinatal transmission of HBV is important in perpetuating the hepatitis B carrier state in endemic countries in Asia. Infection by the HBV early in life leads to the development of chronic hepatitis, cirrhosis, and primary hepatocellular carcinoma during adulthood. Although uncommon among young HBsAg-positive carriers, the cancer does occur during childhood. In this report, we provide convincing evidence that primary hepatic carcinoma developed in an HBsAg-positive child who acquired HBV infection via the perinatal route. Thus, to decrease the perpetuation of this chronic viral infection, preventing the perinatal transmission of HBV is of utmost importance. The availability of hepatitis B immune globulin (HBIG) and the hepa-

titis B vaccine has made this goal possible. Recent studies have shown that administering HBIG and the hepatitis B vaccine to infants born to HBeAg-positive carrier mothers was 85% to 93% effective in preventing HBV infection in these newborn infants.[13-16] The application of such treatment modalities in HBV-endemic areas will significantly reduce the incidence of the carrier state, chronic hepatitis, and primary hepatocellular carcinoma in these populations.

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Severe Hypermagnesemia Due to Multiple-Dose Cathartic Therapy

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DESPITE DEBATE over their efficacy, magnesium-containing cathartics are widely used in the care of poisoned and overdosed patients.[1] Until recently, such patients generally received only a single dose of cathartic early in the course of their management. There have been no reported cases of hypermagnesemia in patients with normal renal function after single-dose cathartic treatment. As a result, Mg-containing cathartics have been considered safe to use.

(Smilkstein MJ, Smolinske SC, Kulig KW, et al: Severe hypermagnesemia due to multiple-dose cathartic therapy. West J Med 1988 Feb; 148:208-211)

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ABBREVIATIONS USED IN TEXT

GFR = glomerular filtration rate
ICU = intensive care unit

In conjunction with multiple-dose activated charcoal therapy, the use of multiple doses of cathartics is now common. Safe dosing limits for Mg have not been investigated for this regimen. We report a case of life-threatening hypermagnesemia in a patient with normal renal function who received excessive Mg during treatment with multiple-dose cathartics.

Report of a Case

The patient, a 56-year-old woman, presented to the emergency department three to four hours after an overdose of several drugs taken in a suicide attempt. At her home, medications unaccounted for included as many as 50 Tylenol #3 (acetaminophen, 300 mg; codeine, 30 mg), 21 Placidyl (ethchlorvynol, unknown mg), 34 Fiorinal (butalbital, 50 mg; aspirin, 325 mg; caffeine, 40 mg), and 84 Atarax (hydroxyzine hydrochloride, 25 mg). Other medications were available but accounted for.

The patient was initially awake, alert, but disoriented. Her speech was garbled and inappropriate. Her vital signs were as follows: pulse 92 per minute, blood pressure 140/78 mm of mercury, respirations 18 per minute, and temperature 37.1°C (98.7°F). The remainder of the physical examination elicited no abnormalities. A complete blood count and values for serum potassium (3.9 mEq per liter), blood urea nitrogen (6 mg per dl), creatinine (0.4 mg per dl), glucose (106 mg per dl), and calcium (8.8 mg per dl) were normal. Qualitative urine toxicology screening was positive for butalbital, phenobarbital, salicylate, ethchlorvynol, acetaminophen, benzodiazepine metabolites, phenylethylamine, codeine, and a diphenhydramine-like substance. Quantitative blood levels were as follows: butalbital 31 μg per ml, phenobarbital 7.9 μg per ml, salicylate < 1.5 mg per dl, ethchlorvynol 6.8 μg per ml, acetaminophen < 2 μg per ml, and benzodiazepine < 0.5 μg per ml. Quantitative levels for the other agents found in the urine were not available.

There was no change after administering 0.8 mg of naloxone hydrochloride intravenously. Gastric lavage recovered pill fragments. She was given 100 grams of activated charcoal and 15 grams magnesium sulfate and admitted to the intensive care unit (ICU).

In the ICU, persistent confusion and agitation were noted. Pupils were dilated but reactive. Vital sign examination showed her pulse to be 98 to 110 per minute, blood pressure 110 to 170/70 to 94 mm of mercury, and respirations 16 to 22 per minute. Treatment initially consisted of intravenous hydration, supplemental oxygen, and 50 grams of activated charcoal in water every two hours. After five hours (nine hours after ingestion), a regimen of 75 grams $MgSO_4$ (150 ml of a 50% solution of $MgSO_4$) given every hour was begun unintentionally. A large diarrheal stool was noted two hours later. Four hours after starting the regimen of $MgSO_4$, lethargy was noted but deep tendon reflexes were present and the patient responded to commands. Two hours later, after the patient had received six doses of $MgSO_4$ (a total of 465 grams

since admission), a cardiorespiratory arrest occurred. At the time of the arrest, bradycardia, coma, apnea, and no palpable blood pressure were noted. Resuscitative efforts included endotracheal intubation and intravenous administration of atropine sulfate and epinephrine. The subsequent course is shown in Figure 1. One and a half hours after the arrest, her serum Mg level was 21.3 mEq per liter (normal 1.5 to 2.5) and calcium was 9.9 mg per dl (normal 8.5 to 10.5). After resuscitation, blood urea nitrogen and creatinine levels were 4 and 0.6 mg per dl, respectively.

Profound hypotension was treated with fluid boluses and the administration of dopamine hydrochloride and norepinephrine bitartrate. During the first six hours following the arrest, 308 mEq of sodium bicarbonate was given. Furosemide, 40 mg, was given intravenously because of a possible fluid overload. Pronounced hypokalemia (1.6 mEq per liter) was noted and treated with potassium replacement. Hyperglycemia ensued (540 mg per dl), and insulin was given. Her urine output was less than 30 ml per hour for the first three hours after her arrest but then gradually increased to 200 to 300 ml per hour seven hours after the arrest. Blood urea nitrogen and creatinine measurements every two to four hours following the arrest remained normal, with maximums of 10 and 0.6 mg per dl, respectively.

Her serum magnesium levels gradually returned to normal with supportive care only (see Figure 1). The patient showed withdrawal to pain 10½ hours after the arrest, followed simple commands 14 hours after the arrest, and the endotracheal tube was removed 31 hours after the arrest.

She remained confused, and hypertension developed, requiring treatment. Her subsequent course was otherwise uneventful, and she recovered completely.

Discussion

In the absence of renal dysfunction, symptomatic hypermagnesemia is unusual, but has occurred after rectal dosing and after combined oral and rectal dosing in patients with bowel obstruction, megacolon, or bowel perforation.[2,3] In patients with renal failure, symptomatic hypermagnesemia has occurred after the use of Mg-containing antacids, cathartics, enemas, parenteral infusions, dialysate, and Renacidin.*[2,3] Until recently,[4] hypermagnesemia after oral Mg administration had not been reported in patients with normal gastrointestinal tracts and renal function. Surprisingly, other than intentional hypermagnesemia for the treatment of eclampsia or preeclampsia, symptomatic hypermagnesemia due to parenteral Mg dosing is infrequent.[2,3]

There have been no reports of Mg toxicity after single-dose cathartic therapy, suggesting that standard doses (see Table 1)[5] are safe when given once. While the use of multiple doses of Mg-containing cathartics is clearly increasing, safe dosing strategies have not been studied.

Magnesium Homeostasis

Normally, 30% to 40% of total dietary Mg—average, 25 mEq per day[6,7]—is absorbed with more (up to 76%) or less (as low as 24%) being absorbed during low and high Mg intake, respectively.[6,8] The fractional absorption of Mg after oral cathartic administration is unknown; 30 grams of $MgSO_4$ contain 2.9 grams (240 mEq) of Mg (see Table 1). Any significant absorption of this amount clearly would require an increase from the baseline renal Mg excretion to maintain a normal Mg concentration. The patient in the present case received 465 grams of $MgSO_4$ (44.6 grams, 3,720 mEq of Mg) over ten hours. About 97% of the dose was given in the last five hours of this period. In the report by Fassler and co-workers of cathartic-induced hypermagnesemia without renal impairment, 90 grams (7,380 mEq) of Mg was given, evenly distributed over an 11-hour period, yielding a Mg level of 13.2 mEq per liter.[4]

Normally, renal Mg excretion amounts to only 100 to 150 mg (8 to 12 mEq) or roughly 3% of the total filtered Mg per day.[7] When hypermagnesemia occurs, renal tubular reabsorption declines, and as much as 97% of filtered Mg is excreted.[7] The maximum Mg load that can be excreted without Mg accumulation and a resultant hypermagnesemia is not known. In patients given 5.6 grams (467 mEq) of Mg per day by mouth, renal excretion increased to 500 to 600 mg (42 to 50 mEq) per day, and normal Mg concentration was maintained; presumably, decreased gastrointestinal fractional absorption limited the absorbed Mg dose to help maintain homeostasis.[6] Six grams (500 mEq) per day has been suggested as an achievable maximum daily Mg excretion.[4] These data are derived from a hypermagnesemic dog model,[9] and its relevance to humans is unknown. One patient with a serum Mg level of 17.3 mEq per liter excreted 196 mg (16.3 mEq) in three hours,[10] but no other data on maximal human excretion capability are available. The degree of renal impairment affects excretion capability. While patients with creatinine clearance values of 30 ml per minute or less are at the greatest risk for the development of hypermagnesemia,[2] life-threatening hypermagnesemia has recently been reported with only minimal renal dysfunction after multiple-dose cathartic therapy in standard doses.[11] In the present case, administering high doses of hypertonic $MgSO_4$ may have led to a significant loss of extracellular fluid into the gastrointestinal tract. Stool losses were not accurately quantified. With or without such intravascular volume loss, decreasing blood pressure due to developing hypermagnesemia probably led to a decreasing glomerular filtration rate (GFR). Such a decrease in the GFR would rapidly result in further Mg accumulation. Although this was almost certainly the case, it remains speculative because there were no hourly urine output determinations before the patient's cardiorespiratory arrest.

Magnesium Toxicity

The signs and symptoms seen in this case were consistent with those seen in cases of severe hypermagnesemia (see Table 2), although the course may have been altered by the apparent anticholinergic overdose (hydroxyzine). Findings were initially attributed to the patient's overdose, and hypermagnesemia was not considered. Deep tendon reflexes disappear at Mg levels of 7 to 10 mEq per liter, respiratory depression and unresponsiveness occur above 9 to 10 mEq per liter, and cardiac arrest is generally seen at levels above 14 to 15 mEq per liter.[2] Two and a half hours before the arrest, the deep tendon reflexes were present and the patient was responsive, suggesting that the subsequent rise in the serum Mg level was rapid. Whether severe hypermagnesemia causes actual coma is unclear. Unless hypermagnesemia is protracted or there is a defect in the blood-brain barrier, the central nervous system is generally not greatly depressed. Unless hypotension, hypoxia, or other metabolic causes of coma are present, the unresponsiveness of patients with severe hypermagne-

*A product used in urolithiasis. Active ingredients: citric acid, anhydrous, and D-gluconic acid (Guardian Chemical, Smithtown, NY).

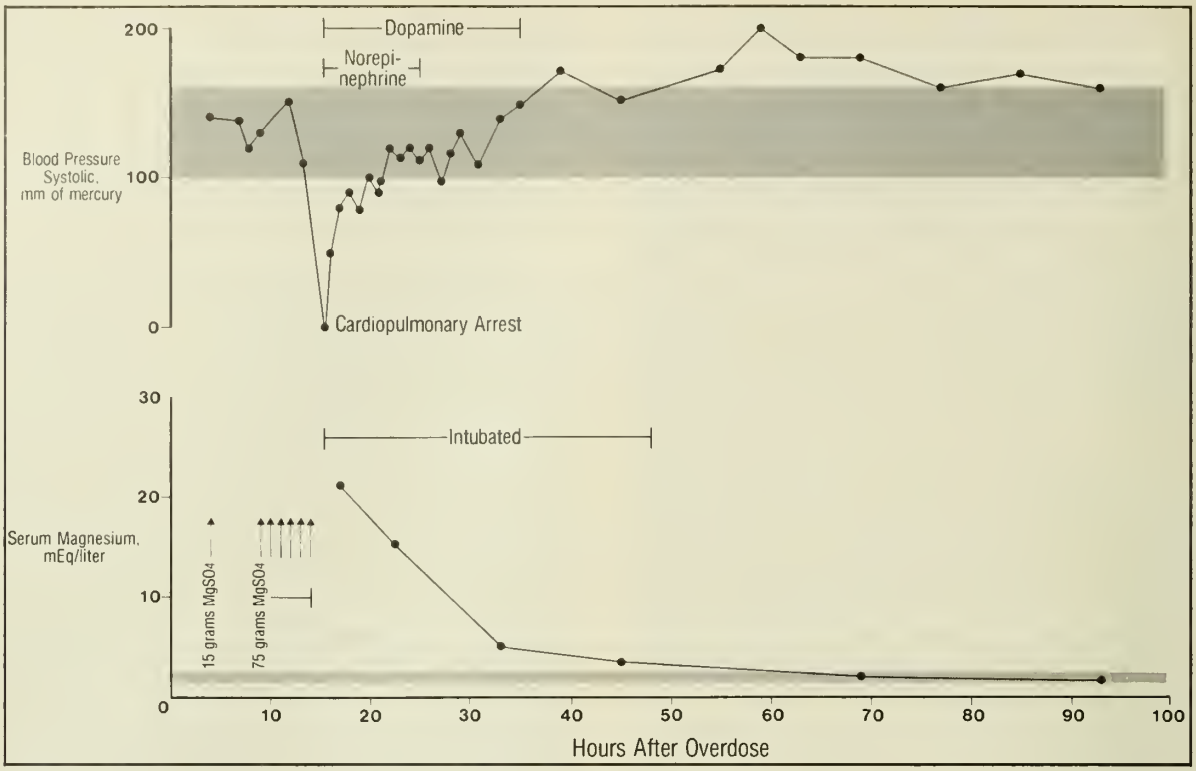

Figure 1.—The graph shows the clinical course and serum magnesium levels in a patient with severe hypermagnesemia due to multiple-dose cathartic therapy. The shaded areas indicate normal ranges.

semia is often due to complete neuromuscular paralysis.[2] Actual central nervous system depression certainly may have occurred in this case due to brain injury from cardiac arrest and hypotension.

The hyperglycemia and hypokalemia were probably not directly due to hypermagnesemia. Although hypermagnesemia inhibits the release and action of endogenous catecholamines,[2] some degree of hyperglycemia would be likely after the high dose of exogenous catecholamines used in this patient's resuscitation and supportive care. Whether or not the resultant hyperglycemia was exacerbated by unsuspected glucose intolerance was unknown at the time of discharge. Although early work suggested that hypermagnesemia might cause hypokalemia, this has not been substantiated.[2] The likely sites of potassium loss in this patient included cathartic-induced diarrhea and urinary losses due to glycosuria, furosemide therapy, and hypotension-induced renal sodium conservation. Certainly sustained hyperglycemia, insulin therapy, and the aggressive use of bicarbonate contributed to hypokalemia by producing intracellular potassium shifts.

The patient's clinical recovery corresponded to the fall in Mg levels (see Figure 1). Once Mg dosing was discontinued and the blood pressure and GFR were adequate to allow renal Mg elimination, levels declined rapidly.

Treatment of severe hypermagnesemia includes discontinuing Mg intake, maintaining normal urine output or hemodialysis if renal impairment is present, supportive measures to correct hypoventilation and hypotension, and administering calcium.[2,3,6] There is no doubt that severe hypermagnesemia should be treated with dialysis in patients with compromised renal function.[2-4,6] As this case shows, however, when renal function and the GFR are adequate, even life-threatening hypermagnesemia can be treated without dialysis.[4] Calcium has been shown to reverse both Mg-induced hypotension and paralysis.[2] Although sustained hypermagnesemia can cause hypocalcemia,[2] calcium levels were normal in this case. Calcium directly antagonizes the effects of hypermagnesemia and is indicated even in patients with normal calcium levels when serious Mg toxicity is present. Calcium was not used in the present case because the diagnosis of hypermagnesemia was not made initially.

TABLE 1.—*Magnesium Content of Standard Cathartic Doses**

Cathartic	*Magnesium Content*	
	Milliequivalent	*Milligram*
Magnesium sulfate solution ($MgSO_4 \times 7\ H_2O$)/gram	8	96
Adult dose, 30 grams	240	2,880
Pediatric dose, 250 mg/kg	2/kg	24/kg
Magnesium citrate ($C_{12}H_{10}Mg_3O_{14}$)/dl	0.8	9.6
Adult dose, 300 ml	240	2,880
Pediatric dose, 4 ml/kg	3.2/kg	38.4/kg

*From Rumack.[5]

TABLE 2.—*Clinical Findings of Hypermagnesemia**

Serum Magnesium, mEq/liter	*Clinical Findings*
3- 9	Hypotension, cutaneous flushing, nausea, vomiting
5-10	Electrocardiographic changes, decreased deep tendon reflexes, central nervous system depression (see text), bradycardia
> 9-10	Respiratory depression, unresponsiveness
>14-15	Asystole, cardiac arrest

*From Mordes and Wacker.[2]

Conclusion

This case provides further evidence that orally adminis-

tered Mg-containing medications can cause hypermagnesemia in patients with normal renal function. With the increasing use of multiple doses of Mg-containing cathartic therapy for poisoned or overdosed patients, more patients will receive higher Mg loads. Safe upper limits for Mg dosage by this route have not been established. Therefore, when treating patients in this manner, physicians should consider monitoring Mg levels and renal function and must be vigilant for signs and symptoms of hypermagnesemia. An alternative is the use of sorbitol[1,5] as a cathartic, although its safety in multiple doses has not been well studied.

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Occult Mineral Oil Pneumonitis in Anorexia Nervosa

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ANOREXIA NERVOSA-BULIMIA is a disorder primarily affecting young, white, middle-class women.[1-3] Due to the altered nutritional state associated with this condition, many secondary medical disorders occur.[4] Associated pulmonary complications are uncommon.[1,2] We present the case of a patient with a previously unreported complication of anorexia nervosa—occult mineral oil aspiration leading to respiratory failure.

Report of a Case

The patient, a 36-year-old woman, had a 20-year history of anorexia nervosa and bulimia associated with diuretic, laxative, and alcohol abuse plus depression with multiple suicide attempts. She was admitted due to the recent development of peripheral edema with a 12-kg (25-lb) weight gain. On physical examination on admission she was unkempt, cachectic, and appeared chronically ill, with ascites and anasarca, but in no acute distress. The cardiopulmonary examination showed no abnormalities. Laboratory evaluation revealed a hematocrit of 33% and abnormal liver function test values, including an albumin of 1.4 mg per dl. The leukocyte count, electrolytes, renal function, chest x-ray film, and an electrocardiogram (ECG) were normal.

Enteral alimentation and vitamin replacement were initiated, with a 3-kg (6-lb) weight gain over the next week. On the seventh hospital day, acute respiratory distress developed, and the patient had a temperature of 38.6°C (101.4°F). She said her only new symptom was dyspnea. On physical examination there were bilateral rales, expiratory wheezes, bibasilar dullness, jugular venous distension with a summation gallop, and anasarca. Laboratory tests showed a hematocrit of 26%, a leukocyte count of 19,600 per μl and arterial blood gas values with the patient breathing 100% oxygen by mask of pH 7.37, a partial carbon dioxide pressure of 44 torr, and a partial oxygen pressure of 62 torr. The ECG was unchanged. A chest x-ray film (Figure 1) showed an increased cardiac size, hilar haziness, bilateral alveolar infiltrates predominantly in the upper lobes, and bilateral pleural effusions. A bilateral thoracentesis revealed transudates, and a sputum Gram's stain showed mixed flora. Vigorous treatment including diuresis, transfusion, bronchodilators, and antibiotic coverage for nosocomial aspiration was initiated.

Despite the above treatment, the patient's condition deteriorated, requiring intubation and mechanical ventilation. Oxygen concentrations in the 70% to 80% range with 10 cm water of positive end-expiratory pressure were initially necessary to maintain adequate oxygenation. A right heart catheterization showed a cardiac output of 6.3 liters per minute and a mean pulmonary artery wedge pressure of 26 mm of mercury. On a gated blood pool study, there was a reduced left ventricular ejection fraction of 52% with no regional wall abnormalities, and an echocardiogram revealed septal dyskinesis, mild generalized hypokinesis, and a small pericardial effusion. Several sputum cultures grew mixed flora.

Five days after intubation, a temperature of 38.5°C (101.3°F) developed, and chest x-ray film findings worsened. A fiberoptic bronchoscopy showed no abnormalities. Trans-

Figure 1.—A chest roentgenogram shows acute respiratory failure with upper lobe pneumonitis and superimposed congestive heart failure.

(Ferguson GT, Miller YE: Occult mineral oil pneumonitis in anorexia nervosa. West J Med 1988 Feb; 148:211-213)

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bronchial biopsy specimens of the lingula revealed diffuse, nonspecific, organizing alveolitis. Cultures and special stains for viral, *Legionella*, mycobacteria, fungal, and *Pneumocystis* infection were all negative. The patient was diuresed to her dry weight, and a seven-day course of antibiotics for aspiration was completed. The endotrachcal tube was removed on the 15th hospital day, with the patient receiving adequate oxygenation on 4 liters per minute of oxygen by cannula plus 40% mist mask. A chest x-ray film (Figure 2) showed a bilateral diffuse interstitial infiltrate. The patient remained stable and was transferred to a ward.

Three days later the patient had increasing dyspnea and hypoxemia. A repeat chest roentgenogram showed increasing alveolar infiltrates. Because of a concern for factitious disease, a room search was undertaken, revealing two bottles of mineral oil. On confrontation, the patient admitted using the mineral oil in her food as a "low-calorie way to get oil in my diet," but said she did not aspirate. The patient's pulmonary state continued to deteriorate. A right heart catheterization showed a normal cardiac output and wedge pressure.

She subsequently underwent a right lower lobe open-lung biopsy. Histologic examination (Figure 3) showed severe lipoid pneumonitis, bronchiolitis, and patchy interstitial fibrosis. A retrospective review of the transbronchial biopsy specimens showed macrophage vacuolization suggestive of lipoid material removed by tissue processing. Postoperatively the patient was surreptitiously observed to volitionally aspirate liquids. She was placed under close observation, and her condition stabilized. Pulmonary function tests showed severe restrictive disease, and 5 liters of oxygen per minute via a nasal cannula was required to maintain adequate oxygenation. Because of her severe disease, a regimen of corticosteroids was started, with 40 mg of prednisone tapered to 10 mg. On her 37th hospital day, she was discharged to an inpatient psychiatric service. Since discharge the patient has progressively improved. Her corticosteroid dosage has been discontinued, and she currently requires oxygen supplementation only with exercise.

Discussion

Pulmonary complications of anorexia nervosa are unusual and have received little attention in the medical literature. Review of the many medical complications associated with eating disorders suggests several possible mechanisms that can contribute to respiratory failure. Although lipoid pneumonia was the major disease process in this patient, there were other potential contributing factors.

Cardiac dysfunction associated with anorexia is well documented.[5-7] Congestive heart failure due to this is generally easily managed but may result in significant pulmonary compromise.[6] Echocardiography in anorexic patients shows a decrease in left ventricle thickness and stroke volume, plus an increase in ventricular dimensions with refeeding, suggesting volume overload due to myocardial dysfunction and an added solute load.[5] Pathologic examination of malnourished patients reveals decreased myocardial muscle mass and fibrosis. An increased cardiac demand due to an anabolic state with refeeding, in conjunction with anemia and thiamine deficiency, can result in high output failure. Other possible contributing factors include hypothyroidism, hypokalemia, hypophosphatemia, and a cardiomyopathy associated with ingesting ipecac.[8-10] In addition, extracellular fluid retention is potentiated by an increased renal sensitivity to aldosterone during refeeding and a decreased oncotic pressure due to hypoalbuminemia.[9,11]

Infection related to malnutrition is well documented. Patients with kwashiorkor and protein-calorie malnutrition have been shown to have cell-mediated and, to a lesser extent, humoral immunodeficiency.[12] In addition, leukopenia and hypocomplementemia are frequently present. Gotch and coworkers reported a granulocyte killing defect in three anorexic patients with staphylococcal infections that resolved with nutritional repletion.[13] A case of anorexia with hypocomplementemia and recurrent cellulitis has been reported.[14] An increased incidence of tuberculosis in men with anorexia nervosa has also been cited.[15] Despite this, in several reviews of medical complications of anorexia nervosa, no increased incidence of recurrent community-acquired or opportunistic infections has been described.[1,3,4] Armstrong-Esther and associates investigated the immune response in anorexic patients and found no cell-mediated or humoral deficiency.[15] A possible explanation is that anorexia nervosa, in contrast to kwashiorkor, is most often a carbohydrate deficiency state with adequate protein stores.[16] In spite of the peripheral neu-

Figure 2.—A chest roentgenogram shows the chronic stage of lipoid pneumonitis with extensive fibrosis.

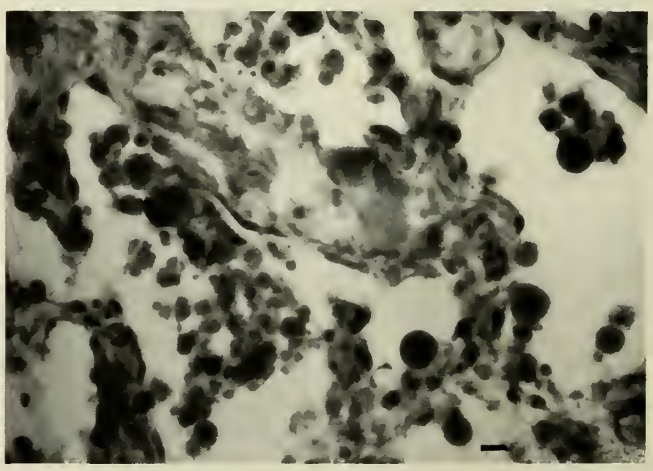

Figure 3.—An open-lung biopsy specimen from the right lower lobe shows extensive lipoid deposition with macrophage phagocytosis and interstitial fibrosis (oil red O stain, original magnification × 200).

tropenia associated with anorexia nervosa, marrow reserves are adequate and there is no increased incidence of associated opportunistic infections.[17]

Another possible cause of pulmonary injury in malnourished patients involves an associated antioxidant deficiency. Glutathione and other similar proteins are depleted in malnourished patients. In animal studies, increased susceptibility to oxygen toxicity occurs with starvation, especially at the oxygen concentrations required to oxygenate our patient.[18,19]

Several behaviors associated with anorexia nervosa and bulimia predispose patients to pulmonary complications. Pneumomediastinum has been reported in association with bulimia.[20] Aspiration of foreign material is also a major concern. Though mentioned in reviews, there are no reports documenting this complication.[4] Self-mutilative behavior without suicidal intent, in addition to alcohol and drug abuse, is frequently seen in bulimic patients.[21] The circumstances surrounding our patient's lipoid pneumonitis suggest a volitional component. The use of mineral oil as a laxative with accidental inhalation or aspiration is also possible.

Exogenous lipoid pneumonia is an unusual pulmonary problem and has not been reported previously in association with anorexia nervosa.[22] Though most often found as a slowly progressive, minimally symptomatic disease process, it occasionally presents as an acute pneumonitis.[23,24] There is a high incidence of secondary infection due to plugging and impaired mucociliary clearance.[25,26] Occasionally the pneumonitis progresses to interstitial fibrosis.[27] Respiratory failure is rare. Several factors mentioned previously may have contributed to this patient's pulmonary disease, although pathologically no other cause could be found. The use of corticosteroids has been suggested as a potential treatment.[28] With corticosteroid treatment, our patient has shown moderate improvement in lung function, suggesting resolution of the acute pneumonitis with residual fibrosis.

Pulmonary disorders in patients with anorexia nervosa are uncommon, though multiple complications can occur. With the frequent abuse of laxatives, including mineral oil, by anorexic patients, lipoid pneumonia may develop more commonly than previously appreciated. The insidious nature of lipoid pneumonia makes this an easily overlooked and potentially severe complication, which requires a high index of suspicion for prompt diagnosis.

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Coexistent Dermatomyositis and Autoimmune Thyroiditis

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DERMATOMYOSITIS is a disease characterized by nonsuppurative inflammation of skeletal muscle and characteristic skin changes. While dermatomyositis-like syndromes due to hypothyroidism have been well described, the occurrence of both hypothyroidism due to autoimmune thyroiditis and dermatomyositis together is not well documented.

We describe the case of a patient with coexistent autoimmune thyroiditis and dermatomyositis, showing clearly that these diseases can coexist. He was treated with pharmacologic doses of both steroids and thyroid hormone and is in clinical remission after two years.

Report of a Case

The patient, a 50-year-old male rice farmer, presented with proximal muscle weakness, Raynaud's phenomenon, dysphagia, hoarseness, and loss of energy for six months. On physical examination he had profound muscle weakness in the limb girdle and neck flexors. The patient was unable to lift his head from the pillow, rise from a chair, or walk up stairs without assistance. No fasciculations were seen. The neurologic examination elicited no abnormalities. Examination of the neck showed no goiter. His skin was remarkable for pronounced periungual erythema, a heliotrope rash over the upper eyelids, and Gottron's papules on the knuckles.

Admission laboratory tests were remarkable for the fol-

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ABBREVIATIONS USED IN TEXT

CK = creatine kinase
EMG = electromyogram/phic
TSH = thyroid-stimulating hormone

lowing values: creatine kinase (CK) 3,172 units per liter (normal 35 to 232); serum aspartate aminotransferase (glutamic-oxaloacetic transaminase) 112 units per liter (normal 0 to 41); lactate dehydrogenase 535 units per liter (normal 60 to 200); aldolase 28 mU per ml (normal 0.5 to 3.1); thyroxine 2.3 μg per dl (normal 5 to 12); free thyroxine index 0.9 (normal 1.7 to 5.4); thyroid-stimulating hormone (TSH) 45.1 IU per ml (normal 0.45 to 6.2); antinuclear antibody positive at 1:1,280 in a nucleolar pattern; antithyroid microsomal antibody positive at 1:1,600 dilution (normal less than 1:100); and antithyroglobulin antibody positive at 1:160 (normal less than 1:10).

A thyroid scan using radioactive iodine showed diffusely low uptake at five hours of 4.2% (normal 5% to 15%) and 24 hours' uptake at 10.6% (normal 12% to 36%). The thyroid size was estimated to be 20 grams. An erythrocyte sedimentation rate, chest x-ray film, electrocardiogram, complete blood count, anti-Smith antibody, anti-double-stranded DNA antibody, complement levels of C3 and C4, and antiribonuclear protein were all negative or normal. The test for the polymyositis-1 antigen was not done. An electromyogram (EMG) was diffusely abnormal with fibrillations, insertional irritability, positive sharp waves, and short-duration action potentials consistent with inflammatory myopathy. A biopsy specimen of the quadriceps showed perifascicular atrophy with lymphatic infiltrations of perifascicular collagen, muscle fascicle necrosis of type 1 and type 2 fibers, and basophilia consistent with polymyositis. An occult carcinoma workup was negative.

Clinical Course

Therapy consisting of the administration of levothyroxine sodium (Synthroid), 0.15 mg per day, and prednisone, 60 mg per day, was started. The CK level came down to 224 units per liter at one month and the TSH was down to 4.1 IU per ml. The prednisone dosage was rapidly tapered to 20 mg per day and at three months the CK value had returned to normal.

Clinically, the patient had quick resolution of his dysphagia, but muscle strength improved only slowly. Attempts to wean the prednisone therapy completely have been unsuccessful, and he is currently maintained on a regimen of 7.5 mg per day. At a two-year follow-up visit, his CK level and thyroid function tests remain normal, and muscle strength is adequate for farming chores.

Discussion

Hypothyroidism has long been associated with muscle weakness. Several authors have described a hypothyroid state clinically mimicking polymyositis/dermatomyositis.[1-6] Differentiating these diseases can be quite difficult, often relying on clinical grounds because laboratory test results can be ambiguous. We are aware of only one case report associating dermatomyositis and autoimmune thyroiditis.[7] Our patient presented with the clinical features of dermatomyositis and was found to have coexistent hypothyroidism due to autoimmune thyroiditis.

This case shows the difficulties of interpreting laboratory data to diagnose these diseases. Muscle enzyme activity can be normal or elevated in both diseases.[8-10] Similarly, EMG studies in hypothyroid patients with myopathy have had a wide variety of findings, from fibrillations and positive sharp waves to normal results,[8,10-14] although recent authors tend to support the view that the EMG should be normal in patients with hypothyroidism.[13] Muscle biopsy specimens from hypothyroid patients have shown such diverse features as lymphocytic infiltrates, basophilia, and focal necrosis,[1,14,15] typically seen in patients with polymyositis, while others have had no pathologic findings.[15(pp642-643)] One conceivable explanation of these ambiguities lies in the possibility that some of those hypothyroid patients with abnormal EMG and muscle biopsy findings may have both diseases coexisting.

Immunologic studies have shown that both of these diseases are autoimmune mediated. Suppressor T-cell dysfunction and lymphocyte-mediated cytotoxicity have been well described in cases of polymyositis,[16] and there is evidence of suppressor T-cell dysfunction in autoimmune thyroiditis as well,[17-19] suggesting a common pathogenesis. In addition, the incidence of histocompatibility antigens HLA-B8 and DR3 is increased in frequency in autoimmune thyroiditis[20] and adult dermatomyositis.[21] In our patient and in that of White and Tesar,[7] hypothyroidism due to autoimmune thyroiditis most likely preceded the onset of dermatomyositis.

In conclusion, it is important for clinicians to be more aware that dermatomyositis and hypothyroidism due to autoimmune thyroiditis can coexist and a thorough evaluation of both may be necessary in patients presenting with proximal muscle weakness. In addition, further studies of the immunologic aspects of both diseases may unravel common pathways of autoimmune-mediated cellular dysfunction.

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Correspondence

Neuromuscular Blockade Due to Gentamicin Sulfate

To THE EDITOR: Iatrogenic disease is difficult to recognize when the clinical condition of a patient may mask a drug's uncommon side effect. We report to your readers a case of probable gentamicin sulfate-induced diaphragmatic paralysis, initially attributed to aspiration pneumonia or "frailty" of old age.

The patient was an 89-year-old man admitted to the hospital for internal fixation of a left femoral neck fracture. After his operation, the patient was transferred to the medical service for treatment of a urinary tract infection. At the time, the patient had a decreased mental status, a temperature of 39.45°C (103°F), and a leukocyte count of 41,200 per ml with a left shift. Urine cultures were positive for *Pseudomonas aeruginosa*. Arterial blood gas measurement made while the patient was breathing room air was pH 7.43, partial pressure of carbon dioxide (P_{CO_2}) 19 torr, and partial pressure of oxygen (P_{O_2}) 57 torr. The patient's medical history was significant for chronic renal failure (creatinine 1.6 mg per dl, blood urea nitrogen [BUN] 37 mg per dl) and congestive heart failure.

Antibacterial therapy was initiated with gentamicin and mezlocillin sodium given intravenously; the patient's temperature decreased and his mental status improved. Laboratory tests showed a decreasing leukocyte count. His creatinine and BUN levels, however, had begun to rise further: 4.5 and 87 mg per dl, respectively; a gentamicin trough concentration was 6.0 mg per dl, and the gentamicin therapy was stopped. Nonetheless, the patient's mental status deteriorated. Examination then revealed shallow breathing, with the patient unable to clear his secretions. The arterial blood gas determination with the patient receiving 2 liters of oxygen was pH 7.19, P_{CO_2} 57 torr, and P_{O_2} 59 torr. A chest x-ray film showed a poor inspiratory effort, with bilateral basilar infiltrates consistent with atelectasis. After intubation and mechanical ventilation, there was an immediate and notable improvement in the patient's mental status and arterial blood gas values; with the patient breathing 50% oxygen, the values were pH 7.36, P_{CO_2} 35 torr, and P_{O_2} 115 torr. The endotracheal tube was removed three days later without complications. The diagnosis of presumed gentamicin-induced respiratory paralysis was made retrospectively, precluding electromyographic studies to verify this diagnosis.

Gentamicin is a commonly used antimicrobial drug. Nephrotoxicity and ototoxicity are usually the feared complications. A less frequently recognized but serious side effect is respiratory depression. In 1956 Pridgen reported four cases of neomycin-induced respiratory arrest.[1] Since then, the use of streptomycin sulfate, kanamycin sulfate, and gentamicin has also been associated with respiratory failure.[2-4] Conditions associated with adverse consequences include intravenous or serosal administration, accidental overdose, renal failure, antecedent neuromuscular disease, or the concomitant use of anesthetics.[3]

Respiratory paralysis has been treated with intravenous calcium or cholinesterase inhibitors such as neostigmine methylsulfate.[2-5] Neither of these agents was administered to this patient. In our opinion, ventilatory support is the primary modality of therapy. Amikacin sulfate was used for further cautious treatment of this patient, and levels were closely monitored. We could not find any reported cases of amikacin-induced respiratory paralysis.

We report this case because elderly patients often have underlying disorders leading to respiratory failure; the possibility of aminoglycoside toxicity as a cause should be entertained, as it is reversible.

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Profession Under Stress

To THE EDITOR: The recent editorial on stress by Dr Watts recounted some of the many reasons we enter the medical profession. When we are under attack on many fronts, as we are today, one does see physicians either redoubling their commitment to our profession or getting out entirely. But you must admit that we are merely in a transitional phase. If the people of the United States allow our government to even more severely restrict the private practice of medicine and, in effect, make us hirelings of government, then you will see a pervasive deterioration of the quality of medicine as talented people elect to choose other vocations where they may receive just compensation for their work. To suggest otherwise—that we physicians will tirelessly toil at our demanding tasks even in the event of harshly restricted economics—flies in the face of the reality of human nature. Change the reward; change the profession.

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Autopsy on an AIDS Patient

To THE EDITOR: On occasion, one is forced to wonder about the purposes of an editorial board of a medical journal when certain articles reach print. This was certainly the case for me on reading "First Case" in the November, 1987, issue.[1]

One is hard-pressed to criticize the author, since the autopsy described was clearly a powerful emotional experience for him. Nonetheless, the drama of the essay strikes one as excessive in view of the available scientific information about AIDS. In addition, the essay seems totally inappropriate for a medical publication.

What is the risk at the time of autopsy? Has a pathologist or any autopsy room personnel, other than those in high risk groups, caught AIDS? The most recent Centers for Disease

Control review of this question does not list such individuals.[2] Has there been a seroconversion related to the autopsy? There is no evidence that this has occurred.

Surely there have been innumerable scratches, skin punctures, mucous membrane exposures, and accidental cuts sustained by pathologists and their assistants in the approximately seven years that AIDS has existed in our major cities. Many pathologists were probably rather cavalier in their practices before the epidemiology of this disorder was understood.

Is the AIDS virus present at the time of death? A study devoted to this question has not yet been reported. A number of autopsies have, however, been sampled to try and detect the presence of the virus. The virus is recoverable in many cases, but in very low concentrations (D. Ho, MD, oral communication, 1987).

It was gratifying to read, at the end of the essay, that Dr. Schneiderman had performed seven additional autopsies on AIDS patients with, I am sure, much less fanfare and anxiety. There are, regrettably, a number of pathologists who would not perform autopsies on AIDS patients if they had the choice. They are surely deluding themselves, since there will be, in the coming years, many individuals who come to autopsy without an established clinical diagnosis, or even a clinical suspicion, of AIDS, but who harbor the virus. The answer, of course, is for a greater number of autopsies to be performed, with appropriate precautions, and for the knowledge gained from these cases to be utilized in the better care of patients.

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Rabies

How do you get rabies? The primary reservoir in the United States is the sylvatic reservoir—about 80%. Skunks, foxes, bats, and raccoons account for about 95% of the cases of exposure to human rabies. Dog and cat contributions are very small.

In Minnesota, skunks are invariably number one, but cattle sometimes take over the number one spot. What happens is a rabid skunk gets loose in a pasture of cows and goes around nipping all the cows. Most of the large animals, cows and horses, are not immunized because it's not feasible economically to do so. Also, these animals don't respond well to immunization for the rabies virus.

To get rabies, you've got to have a break in the skin layer. Also, though, mucous membrane contact can cause rabies, so you've got that farm kid who's feeding his rabid horse and the horse is spewing saliva, or the kid with the multiple small scratches and cuts and abrasions on his hands and the pet horse turns out to have rabies. Those are also risk exposures. There's less chance, but you still have to treat that as a rabies exposure.

Maybe you're not going to see rabies, but you may be involved in the decision to treat. Some factors you should bear in mind: There's only a 40% chance if you get bitten by a rabid animal of actually developing rabies. It's not 100% sure that if you get bitten by a rabid bat, you're going to develop rabies.

This came from an Iranian wolf study in the middle 1970s. What happened was that Peace Corps volunteers were serving as medical workers in a remote Iranian village when the monsoon season hit. The rains wiped out all their communication, knocked down the bridges, and a pack of seven rabid wolves got loose in this large village, and went through and just bit everybody up. They ended up with about 74 people who had significant bites. They eliminated all the minor scratches and minor wounds and counted just those people that had big tearing injuries from wolf bites. Of those people, only 40% went on to develop rabies and die. So you probably only have a 40% chance. On the other hand, even though you've got a 40% chance, if you get rabies, you're dead. That's what I tell people—rabies is a fatal disease. If you get it, basically, you're dead.

—ROBERT D. DAHMS, MD

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Topics in Primary Care Medicine

Carpal Tunnel Syndrome

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Carpal tunnel syndrome is a common and potentially disabling condition. When suspected, the diagnosis can be readily made on clinical evidence without the need for extensive ancillary tests. Primary physicians should be able to manage most patients with medical therapy. Patients for whom medical treatment fails or who present with weakness or thenar atrophy should be referred to a competent hand surgeon. Most patients can expect to have a good outcome if the diagnosis is made early, appropriate therapy is instituted, and a periodic reassessment is done to guide further clinical decisions.

"Topics in Primary Care Medicine" presents articles on common diagnostic or therapeutic problems encountered in primary care practice. Physicians interested in contributing to the series are encouraged to contact the series' editors.

BERNARD LO, MD
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Series' Editors

The carpal tunnel syndrome is a potentially disabling compression neuropathy of the median nerve at the wrist. Paget (1854) is credited with the first, albeit atypical, case description of a male patient with a healing fracture of the distal radius. The syndrome was fully described by Hunt in 1909 and 1911 in case reviews of occupationally acquired median nerve compression neuritis leading to thenar atrophy. In 1913, Marie and Foix, drawing on anatomic observations, suggested treating the carpal tunnel syndrome by sectioning the transverse carpal ligament to decompress the median nerve, but the first surgical procedure was not reported until 1946.

Although the prevalence of the carpal tunnel syndrome is uncertain, the anecdotal experience of physicians and the ease with which large series of patients have been accumulated for study would suggest that it is a relatively common condition. If the syndrome is unrecognized by a primary care physician, the result is unnecessary pain and possible disability for patients.

The carpal tunnel syndrome can be easily diagnosed, and effective medical and surgical treatments are available. We will discuss the general approach to diagnosis and management of this syndrome. Indications for diagnostic testing and surgical referral will also be reviewed.

Etiology

The carpal tunnel is a narrow, bony canal containing the median nerve and nine flexor tendons. The fibrous, transverse carpal ligament acts to contain these structures. Any process that leads to an increase in the volume of the canal or reduces its cross-sectional area may cause compression of the median nerve and, if sustained, the carpal tunnel syndrome. Vascular compromise, especially obstruction of venous return causing edema of the nerve, is likely the final common pathway leading to the syndrome.

Many systemic and local processes have been found in association with this disorder (Table 1). The most common of these are overuse of the hands (occupational), pregnancy, using oral contraceptives, inflammatory arthritis or synovitis (especially rheumatoid arthritis), fractures, and diabetes mellitus. Other associated conditions are rare, and more than 50% of cases are idiopathic.

Clinical Presentation

The carpal tunnel syndrome is predominantly a disease of women, with a male to female ratio of about 1:2. More than half of those affected present between the ages of 40 and 60 and within two years of the onset of symptoms.

The carpal tunnel syndrome should be considered in any patient having neuropathic signs and symptoms in the distribution of the median nerve. Pain, numbness, or hyperesthesia distal to the wrist is present in most patients. Although classically confined to the palmar and dorsal surfaces of the first three fingers and lateral aspect of the fourth finger, some patients describe involvement of the entire hand. Weakness or atrophy of the muscles comprising the thenar eminence (opponens pollicis and abductor pollicis) may be seen in more advanced cases. All of these abnormalities may contribute to clumsiness in fine motor activity of the affected hand(s). Although frequently bilateral, symptoms are often most prominent in the dominant hand. Pain proximal to the wrist and extending as far as the shoulder occurs in as many as 30% of

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patients and may be the only complaint on initial evaluation. Symptoms occur both at rest and with sustained use of the hands, especially when this requires significant flexion or extension at the wrist. Pain or nocturnal paresthesias that awaken the patient from sleep are common.

Evaluation

The carpal tunnel syndrome can be diagnosed clinically when patients present with characteristic symptoms and findings. A physician should inquire as to the duration of symptoms, their distribution (including complaints proximal to the wrist), functional limitations, and exacerbating or alleviating factors. The review of systems should focus on the more common conditions associated with the syndrome (Table 1) and other disorders that are part of the differential diagnosis (Table 2). Conditions that may mimic the syndrome include cervical radiculopathy, hyperventilation, and the peripheral neuropathies—especially those due to alcoholism and diabetes mellitus.

A physical examination should begin with inspection of the involved hand(s) and wrist(s) for obvious abnormalities. Because the carpal tunnel syndrome is frequently bilateral, both hands should be evaluated even if only one is symptomatic. The presence of thenar atrophy is indicative of advanced disease. One particularly interesting sign, first described by Phalen, is the volar "hot dog." With extension of the wrist an area of swelling is visible extending proximally from the distal palmar crease medial to the palmaris longus tendon. Because the volar "hot dog" is located at the proximal extension of the ulnar bursa, it is believed to reflect swelling that occurs as the bursa is compressed along with the median nerve.

The strength of the opponens pollicis and abductor pollicis should be evaluated. The opponens pollicis can be tested by having the patient attempt to oppose the thumb and little finger with the examiner's finger offering resistance to the thumb. To evaluate the abductor pollicis, the patient's hand should be resting flat on its dorsal surface with the thumb lying flat along the lateral edge of the palm. The patient is then asked to raise the thumb from the palm against resistance.

Most patients with the carpal tunnel syndrome do not have evidence of atrophy or weakness. Phalen's and Tinel's signs, both provocative tests, are useful in these cases. Phalen's sign refers to the reproduction of a patient's symptoms with maximal flexion of the wrist for about one minute. This can best be accomplished by having the patient press the dorsal surfaces of the hands firmly together with the fingers directed downwards. Tinel's sign involves gentle percussion with a reflex hammer or the examiner's fingers over the volar aspect of the wrist in the general area of the flexion creases. If either sign is positive, the patient experiences paresthesias in the distribution of the median nerve. Phalen's sign, Tinel's sign, or the volar hot dog have been reported to occur separately in 70% to 80% of patients with the carpal tunnel syndrome and appear to be highly correlated with each other.

Further examination should focus on associated conditions or those that may mimic the syndrome that have been suggested by the history and review of systems.

TABLE 1.—*Conditions Associated With the Carpal Tunnel Syndrome*

Idiopathic (>50%)	
Local conditions of the wrist	Systemic conditions
Anatomic anomalies	Acromegaly
Carpal dislocation*	Amyloidosis
Fibrosis	Using birth control drug*
Fractures*	Diabetes mellitus*
Ganglion	Hypothyroidism
Hematoma	Inflammatory arthritis*
Infection	Maintenance hemodialysis
Lipoma	Myeloma
Neuroma	Polymyalgia rheumatica
Osteophytes	Pregnancy*
Overuse of hands (occupational)*	Sarcoidosis
Synovial cyst	
Synovitis*	

*Indicates more common conditions.

TABLE 2.—*Conditions That May Mimic the Carpal Tunnel Syndrome*

Cervical radiculopathy*
Hyperventilation*
Multiple sclerosis
Peripheral neuropathy
Alcoholism*
Diabetes*
Heavy metal intoxication
Hemodialysis
Hypo/hyperparathyroidism
Hypo/hyperthyroidism
Pronator syndrome
Spinal cord tumor
Syringomyelia
Thoracic outlet syndrome
Vascular insufficiency

*Indicates more common conditions.

Diagnostic Testing

Various schemes have been suggested for the use of diagnostic tests in the carpal tunnel syndrome. Often these include screening blood tests for rheumatologic disease, diabetes, and thyroid and parathyroid abnormalities. Roentgenograms of the wrist, cervical spine, and chest are also advocated.

Prospective information regarding the predictive value and cost-effectiveness of these diagnostic modalities is lacking. It is obviously impractical to rule out all conditions that may be associated with or mimic the carpal tunnel syndrome. In most patients, initial treatment should be symptomatic and does not require specific knowledge of the underlying cause. Only those conditions suggested by a patient's history or by physical examination should be pursued with an appropriate diagnostic evaluation.

Electrodiagnostic studies can be an important adjunct to clinical decision making when the diagnosis is in question, or to establish the presence of a process coexisting with the carpal tunnel syndrome. Patients with shoulder pain, for example, may have cervical compression neuropathy as well as the carpal tunnel syndrome.

Electrodiagnostic studies include nerve conduction velocity testing and electromyography. The electromyogram is abnormal in only 45% of patients with the carpal tunnel syndrome. Nerve conduction velocities of interest in the disorder are the distal motor latency and the distal sensory latency. Both are measured across the wrist. The distal motor

latency is abnormal (>4.5 ms) in 69% of patients with the carpal tunnel syndrome, and the distal sensory latency is abnormal (>3.5 ms) in about 90%. The distal sensory latency is, therefore, the most sensitive measurement for confirming the diagnosis of the carpal tunnel syndrome.

Many, but not all, hand surgeons require a nerve conduction velocity study be done before surgical intervention to confirm the diagnosis. There is no evidence, however, supporting serial nerve conduction velocity testing to predict when an operation will be necessary for a given patient.

Treatment

Conservative medical therapy is the rule as long as there is no evidence of motor weakness or atrophy. The goals of therapy should be to alleviate symptoms and preserve normal hand function. In one series of 105 patients with 160 involved hands treated medically, 65% showed no clinical or electrical deterioration after three years of follow-up. This is comparable to other reports and suggests that chronicity should not preclude medical management.

The involved hand(s) should be rested. This is particularly true when an occupational factor is identified, but should be tried in all patients. Volar splinting is an important adjunct to enforce hand rest and is especially useful for those with nocturnal paresthesias or pain. Splints are available by prescription in orthopedic and medical supply houses. Physical and occupational therapists can custom fit splints made from lightweight materials that are often less clumsy for the patient to wear. The use of splints may be limited to nighttime, but some patients may benefit from intermittent splinting during the day. Naturally, coexisting medical problems that may cause or contribute to the symptoms of the carpal tunnel syndrome should be treated.

In patients who do not experience significant relief of symptoms after one to two weeks of splinting, a nonsteroidal anti-inflammatory drug may be prescribed for an additional one to two weeks. The short-term use of a diuretic may also be appropriate if fluid retention is a precipitating factor. If symptoms persist after an adequate trial of rest and medication, injecting the carpal tunnel with steroids can lead to dramatic and long-term resolution of symptoms. This is a simple office procedure that can be done by a primary physician.

A 23- to 25-gauge needle should be used with a small-volume syringe. A solution of 1% to 2% lidocaine without epinephrine, 0.5 to 1 ml, and a similar amount (10 to 20 mg) of a long-acting corticosteroid such as prednisolone acetate are recommended for the injection. Larger volumes should be avoided so as not to increase pressure in the carpal tunnel. The patient is asked to actively oppose the thumb and little finger with slight flexion of the wrist. This maneuver exposes the palmaris longus tendon at the base of the hand. The needle should be aimed toward the fingers at a shallow (about 30-degree) angle to the skin and inserted just medial to the tendon at the distal wrist flexion crease (Figure 1). After advancing the needle 1 cm, the contents of the syringe should be slowly injected. Care should be taken to avoid injecting directly into a blood vessel, the median nerve, or tendons. This can best be accomplished by aspirating before injecting and repositioning the needle if blood is obtained, the patient reports paresthesias, or if more than gentle pressure on the plunger is required.

The patient should be informed that the lidocaine will cause early numbness in a median nerve distribution that will last for a few hours. The carpal tunnel symptoms may then recur, and occasionally a rebound phenomenon occurs with increased pain and paresthesias for 24 to 48 hours. The maximal steroid effect may not be appreciated for a few days. If there is no response, the injection may be repeated after one to two weeks. Injection is unlikely to be effective if it has failed after three or four attempts in a single course of treatment. In addition to the rebound phenomenon, other possible side effects of the injection include a loss of skin pigment at the injection site that may be permanent and, rarely, infection.

All patients should be reevaluated periodically. Control of symptoms should be noted, and patients should be asked about their ability to perform tasks requiring fine motor control of the hands. The thenar muscles should be examined for weakness and evidence of atrophy. If there has been no improvement in sensory complaints, a primary physician should first review the case and decide if the diagnosis is correct. If uncertainty exists, nerve conduction velocity testing should be done to confirm or exclude the diagnosis. Patients with the carpal tunnel syndrome who show inadequate control of symptoms or in whom motor involvement develops should be considered medical treatment failures.

A surgical consultation should be obtained for patients fail-

Figure 1.—Injection of the carpal tunnel is achieved with a 23- to 25-gauge needle and a small-volume syringe filled with 0.5 to 1 ml of 1% to 2% lidocaine without epinephrine and a similar amount (10 to 20 mg) of a long-acting corticosteroid such as prednisolone acetate. The injection is made medial to the palmaris longus tendon (raised midline structure) at the distal wrist flexion crease. The needle should be aimed toward the fingers at a shallow, approximately 30-degree, angle to the skin with the beveled edge up.

ing medical management or presenting with evidence of weakness or thenar atrophy. Various case series have suggested that 30% to 40% of patients will eventually require surgical intervention. Using prognostic factors such as the duration of symptoms, age, and electrodiagnostic studies has been proposed, but none have been shown to aid in the selection of surgical candidates.

Carpal tunnel decompression is generally done on a come-and-go basis in the outpatient surgical department. Regional anesthesia is usually used, with hemostasis maintained by the application of a mechanical tourniquet. Patients with bilateral involvement should generally have the most symptomatic hand treated first and return for a second procedure on the remaining hand, if necessary. A primary physician should refer patients to a hand surgeon who has experience with the procedure after evaluating the surgeon's success rate, complication rate, and average period of recuperation. This information will be of value when discussing a surgical referral with the patient.

In general, the results of surgical treatment are best in patients with primarily sensory complaints. Total relief of symptoms is seen in about 50% of patients while an additional 40% experience fair to good outcomes. As many as 10% report no improvement or, occasionally, more severe symptoms. Patients with established thenar atrophy have the least favorable results, with as many as 30% showing no improvement, emphasizing the importance of referring patients for whom medical management has failed before motor involvement is evident. A repeat operation is rarely indicated but may be a consideration for the few patients who have worsening symptoms or evidence of progressive thenar atrophy after the initial procedure.

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Cataracts and Lasers

CAN CATARACTS BE REMOVED BY A LASER? There is no laser on this earth today that can remove a cataract. There are lasers that can put holes in cataracts. There are lasers that can put holes in the membranes in front of the cataracts. There are experimental lasers that can break up the cataract into smaller pieces. But, as of right now, there is no ophthalmologist on this earth who uses a laser to remove cataracts. And yet, how many times a day do we all hear from our patients, "Gee, my Aunt Tillie had her cataract removed with a laser."

—PERRY S. BINDER, MD

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Health Care Delivery

Training Primary Care Physicians in Flexible Sigmoidoscopy—Performance Evaluation of 17,167 Procedures

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The flexible fiber-optic sigmoidoscope is rapidly replacing the rigid sigmoidoscope in routine screening for colorectal cancer. This study was undertaken to evaluate the safety, usage pattern, and efficacy of fiber-optic sigmoidoscopy by evaluating the outcome of training and the results of procedures carried out by a group of primary care physicians. Of 1,153 participants in one-day flexible sigmoidoscopy workshops, 764 (66%) returned questionnaires evaluating their experiences following this training. Of these, 438 physicians had obtained a flexible sigmoidoscope, used it frequently, and had done a total of 17,167 examinations. The average time of scope usage was nine months. Although additional supervised training was suggested at the time of the workshop, 68% of physicians began doing flexible sigmoidoscopy without it. A total of 465 polyps and 153 cancers were detected by the study group for an overall detection rate of 2.7% for polyps and 0.9% for cancers. Four complications were reported. This study indicates that the technique of flexible sigmoidoscopy is readily learned, is diagnostically productive, and is reasonably safe in the hands of primary care physicians.

(Groveman HD, Sanowski RA, Klauber MR: Training primary care physicians in flexible sigmoidoscopy—Performance evaluation of 17,167 procedures. West J Med 1988 Feb; 148:221-224)

While an ideal cost-effective screening test for detecting colorectal cancer is not yet available, testing a stool specimen for occult blood and doing a sigmoidoscopy are still the mainstays for early detection of malignant and premalignant lesions in asymptomatic persons.[1] The rigid sigmoidoscope has been poorly accepted as a screening instrument primarily because of patient discomfort[2] and the fact that the anatomic distribution of neoplastic lesions within the colon suggests that most are not within the scope's reach.[3]

Several authors have found that the flexible sigmoidoscope has distinct advantages over its rigid predecessor, including a pronounced decrease in patient discomfort and a considerably better diagnostic yield.[4-6] Physicians' acceptance that the procedure can be readily done in their offices has also helped to establish flexible sigmoidoscopy as a viable screening test. A recent survey by the American Cancer Society indicated that 24% of primary care physicians own a flexible sigmoidoscope and that an additional 12% plan to get one.[7]

The extent and type of training in flexible sigmoidoscopy, however, and incidence of complications with the use of this instrument remain controversial.[3,8] This study was designed to address these questions by evaluating the outcome of training and the results of flexible sigmoidoscopy procedures done by a group of primary care physicians.

Methods

Intensive one-day workshops on colon cancer screening were attended by 1,153 primary care physicians. The course content was uniform for all participants and included lectures on colon cancer screening, colon anatomy and pathology, colon polyps, anorectal pathology, and biopsy techniques. Demonstrations of the flexible sigmoidoscope, videotapes on the techniques of flexible sigmoidoscopy, hands-on supervised instruction with the instrument using anatomic models, and workshops on the care and maintenance of the scopes were included. A total of 613 participants attended one of six single-day courses sponsored by the American Cancer Society, and 540 participants attended the program as part of a three-day university course on gastroenterology.

Following the program, questionnaires were distributed to all course participants requesting detailed information concerning their experiences. The questionnaire was developed to gather information regarding the type of physician practice and what prompted the physicians to begin using flexible sigmoidoscopy. Questions addressed the nature and degree of additional supervised training, the number of procedures done, an estimate of patients' acceptance, and the location and type of lesions detected. We sought to elicit information about all flexible sigmoidoscopic examinations, including those done for screening as well as for the evaluation of symptoms. A second questionnaire was mailed to all initial nonresponders.

The signed-rank test was used to compare pretraining and postraining scope usage. Independent proportions were tested using Pearson's χ^2 with Yates's correction; matched proportions were tested using McNemar's χ^2.[9]

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Results

Data forms were collected from 764 physicians (66% response rate). The specialty practice of responders is presented in Figure 1; mean age of the group was 44.8 years. Of the 764 respondents, 126 (16%) started doing flexible sigmoidoscopy before the workshop experience, 354 (46%) began flexible sigmoidoscopy following the workshop, 168 (22%) had not yet obtained an instrument but were planning to begin flexible sigmoidoscopy, 114 (15%) were not planning to obtain a scope, and 2 were unsure. Reasons given for not doing flexible sigmoidoscopy were high instrument cost and anticipated infrequent use. Of the responders, 267 chose to obtain a 65-cm instrument and 203 a 35-cm instrument. The length of flexible sigmoidoscope used by ten physicians was unknown. The mean time of the procedure, distance of scope insertion, months of instrument usage, and number of procedures perceived to be necessary to gain proficiency were compared for 35-cm and 65-cm users and are presented in Table 1.

Overall detection rates for polyps and cancers were nearly identical for those using the 35-cm and 65-cm instruments. A total of 56 polyps and 14 cancers, however, were detected by those using 65-cm instruments beyond 35 cm. These 14 cancers represented 14% of the cancers found by 65-cm scope users. The type and location of detected lesions and detection rates are presented in Tables 2 and 3.

Users of the 35-cm flexible sigmoidoscope found 34% of pathologic lesions at a depth of 20 to 35 cm compared with 54% (of lesions, 0 to 35 cm) for the 65-cm users ($P < .001$ by continuity corrected χ^2). The detection rates for pathologic conditions in the 20- to 35-cm range are identical for 35-cm and 65-cm users (1.2%); thus, the difference is explained by a lower detection rate for 65-cm users versus 35-cm users at 0 to 19 cm (1.1% versus 2.3%).

Four complications were reported—two cases of bleeding that resolved spontaneously but that required transfusion, and two cases of instrument perforations of the sigmoid colon (Table 4). One of these cases resolved following admission to hospital and intravenous administration of antibiotics, but the second patient required surgical repair. No deaths were reported. All four complications occurred in patients examined with the 65-cm scope.

The 438 physicians reporting their procedures had carried out a total of 17,167 flexible sigmoidoscopic examinations or

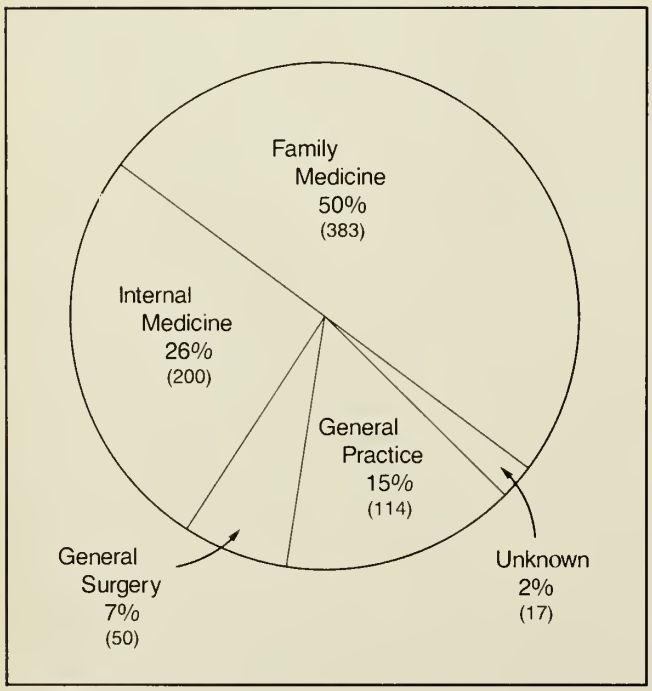

Figure 1.—The specialty of 764 participants who responded to a questionnaire seeking to evaluate their experiences following a one-day workshop on flexible sigmoidoscopy is broken down by percentages. The numbers in parentheses represent the number of responders.

TABLE 1.—*Performance Data for 35-cm and 65-cm Flexible Sigmoidoscopes*

Performance	*Flexible Sigmoidoscope* 35 cm	65 cm
Procedure time, min	16.2	18.6
Length of insertion, cm	28.2	45.3
Months of instrument use	7.8	9.8
No. procedures to become proficient	15.9	15.6

TABLE 2.—*Pathologic Lesions (Polyps) Detected by Scope Length*

Cases	*All Users**	*Flexible Sigmoidoscope* 35 cm	65 cm
No. procedures	17,167	5,296	11,614
No. polyps	465	159	300
Polyp detection rate	2.71	3.00	2.58
Polyp location, cm			
0-19	173	90	83
20-35	156	48	104
36-65	57	..	56
Not reported	79	21	57

*Totals for all users may exceed those for 35- and 65-cm users combined because the length of instrument used by 10 physicians was unknown.

TABLE 3.—*Pathologic Lesions (Cancer) Detected by Scope Length*

Cases	*All Users**	*Flexible Sigmoidoscope* 35 cm	65 cm
No. procedures	17,167	5,296	11,614
No. cancers	153	49	102
Cancer detection rate	0.89	0.93	0.88
Cancer location, cm			
0-19	73	33	39
20-35	53	14	39
36-65	14	..	14
Not reported	13	2	10

*Totals for all users may exceed those for 35- and 65-cm users combined because the length of instrument used by 10 physicians was unknown.

TABLE 4.—*Complications of Fiber-optic Sigmoidoscpy*

Cases	*All Users**	*Flexible Sigmoidoscope* 35 cm	65 cm
Procedures	17,167	5,296	11,614
Deaths	0	0	0
Hemorrhage	2	0	2†
Perforation	2	0	2‡

*Totals for all users may exceed those for 35- and 65-cm users combined because the length of instrument used by 10 physicians was unknown.
†Both patients required transfusions.
‡One patient required surgical repair.

an average of 39.1 per physician. The mean number of "screening" procedures per month was higher for flexible sigmoidoscope users compared with the same group's prior experience with the rigid scope (3.82 versus 2.81, $P < .001$ by the signed-rank test). The physicians overwhelmingly rated patients' acceptance of flexible sigmoidoscopy higher than that for the rigid scope in patients who had previously had this examination.

The type and degree of additional supervised training the physicians received following the workshop and before beginning flexible sigmoidoscopy are presented in Figure 2.

Discussion

This study shows that most physicians who participated in one-day flexible sigmoidoscopy workshops began using this technique in their practice. Those using flexible sigmoidoscopy not only reported the procedure to be more acceptable for patients, but practitioners also increased their screening behavior compared with their prior experience with the rigid scope. There are admittedly limitations and uncontrolled variables in a study that relies on self-reporting of outcomes, but the value of this largely descriptive study lies in the number of participants involved and the volume of procedures reported.

Although participants thought that it requires 15 procedures to become proficient in the technique of flexible sigmoidoscopy, 68% of those who began doing the procedure following the workshop did not or could not obtain the recommended additional supervised training. This finding is very similar to that in a report by Bowman and Wherry, in which 50 of 75 one-day-workshop participants did not receive additional supervision before beginning to do the procedure.[10] These data suggest that flexible sigmoidoscopy is readily learned and may not require intensive postworkshop supervision. Yet, the data do not support abandoning the goal of additional guided instruction in a clinical setting. Hawes and colleagues have shown that despite extensive instruction and practice on a colon model, only 19% of the initial ten 65-cm examinations by residents could be deemed competent.[11] In fact, when grading such variables as insertion distance, procedure time, and diagnostic accuracy, even residents with prior experience in rigid sigmoidoscopy required 24 to 27 examinations before 90% of those examinations were graded as competent. The American Society for Gastrointestinal Endoscopy and the American Academy of Family Physicians recently joined together to formulate a program in which family physicians may learn flexible sigmoidoscopy under the supervision of experienced endoscopists. This is certainly a positive plan, but it remains to be determined if and how this program will affect a large number of primary care physicians.

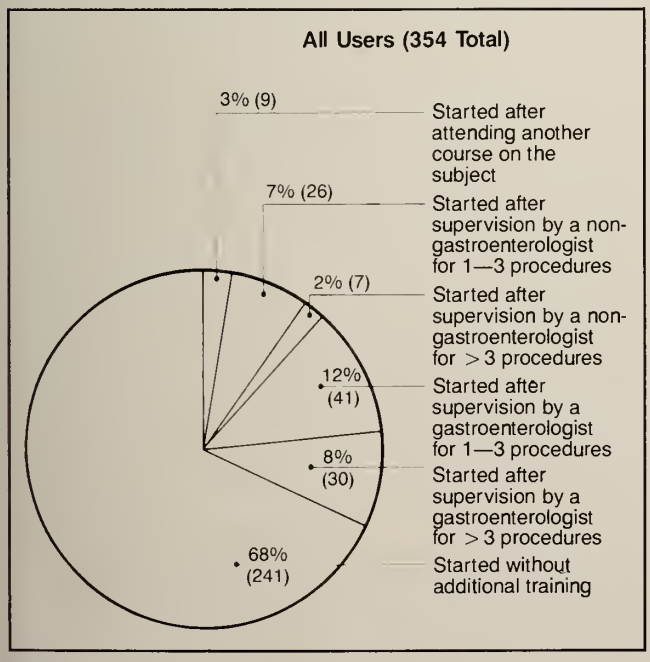

Figure 2.—The graph shows the type and degree of additional supervised training in flexible sigmoidoscopy following the workshop series and before beginning examinations.

This study also shows that the flexible sigmoidoscope is diagnostically productive in the hands of primary care physicians. Although the reported detection rate for polyps varies widely in the literature, the cancer detection rate of 0.9% in this study compares favorably with reports by both primary care physicians and experienced endoscopists.[5,12] The detection of lesions between 36 and 65 cm by the users of the longer scope is expected, but it is not clear to us why there was a lower detection rate for polyps and cancer in the 0- to 19-cm range for users of 65-cm instruments. Perhaps in an examination that takes longer, a hurried (and therefore less accurate) examination is done in the 0- to 19-cm range—the section of bowel that is easiest to negotiate.

The choice of the 65-cm flexible sigmoidoscope by a majority of study participants is in keeping with the current trend toward this length of instrument for primary care physicians. In the study by Bowman and Wherry, 70% of their trainees used the longer scopes after their one-day course.[10] Few instrument companies are currently manufacturing the shorter instruments, and in the next few years these will likely pass out of use. Although our study showed a similar overall lesion detection rate for users of the 35-cm and 65-cm scopes, the potential for a small but significant increase in yield exists with the use of the 65-cm scope.[8,13] Part of the similarity in detection rates in our study may be because the mean insertion distance for 65-cm scope users was only 45.3 cm. In the study by Hawes and co-workers, insertion distance was directly related to experience and reached 45 cm after physicians had done 25 to 27 procedures using the 65-cm scope.[11] Further experience by our trainees presumably might improve their insertion distance and perhaps their diagnostic yield as well. In addition, studies that have documented the position of the instrument tip, either using metal clips or radiographic means, have shown that insertion distance may not correlate with the anatomic extent of the examination.[14,15] Lehman and associates showed that the 60-cm examination viewed 95% of the sigmoid colon surface, while the 30- to 35-cm examination viewed only 53%.[14] These data also point to the 65-cm scope as the screening instrument of choice.

Complications of flexible sigmoidoscopy are rare,[16,17] and it is reassuring that the perforation rate in our study appears to be as low as that reported for rigid sigmoidoscopy.[18] The exact incidence of perforation is unknown, but Sanowski in a review of the subject found one perforation reported in more than 10,000 procedures reported in the literature.[19] Traul and co-workers reported on 5,000 examinations.[20] They described no perforations but indicated that eight persons bled following polypectomy. The fact that all reported complications in our study occurred in the group using the longer scope

is most likely explained by the larger number of procedures in that group and perhaps by an increased risk in examinations that cover a greater anatomic extent.

The value of flexible sigmoidoscopy is in the office-based routine screening for malignant and premalignant lesions of the colon in patients older than 50 years. Physicians who are considering doing flexible sigmoidoscopy should be reassured that this procedure is not a passing fad, that it is reasonably safe, and that its diagnostic yield has the potential for saving lives. Training in the technique might appropriately begin with a short workshop on the subject, but trainees should seek supervised instruction by physicians experienced in doing the procedure safely.

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Special Article

Impact of Urban Disaster on a University Trauma Center

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On the eve of the 1984 Summer Olympics, a deranged man drove his car at high speed onto a pedestrian-crowded sidewalk in a suburb of Los Angeles. The UCLA Medical Center, located two blocks from the scene, received 17 of 51 casualties. One patient arrived in full cardiac arrest and could not be resuscitated. Six had minor injuries or temporary hysteria and did not require admission to hospital. The mean injury severity score of the 10 patients who were admitted was 13.6 (range 3 to 48). Three patients required immediate surgical procedures, and two had delayed orthopedic operations. Specialty consultations were needed in orthopedics, neurosurgery, plastic surgery, otolaryngology, pediatric surgery, and pediatric intensive care. There were no subsequent deaths, although two patients had substantial residual neurologic disability. This episode of unexpected urban violence underscores the need for dedicated trauma services in university centers. Functions of such services include disaster planning, deploying surgical personnel, managing injured patients, and analyzing outcomes.

(Hiatt JR, Larmon B: Impact of urban disaster on a university trauma center. West J Med 1988 Feb; 148:225-227)

Whether in response to a violent attack, a natural event, or a human-created catastrophe, disaster management challenges trauma centers and trauma systems. We analyzed the effects of an unanticipated act of violence on the workings of our trauma center to identify the features and stresses unique to such an episode.

The Incident

At about 9 PM on July 27, 1984, the eve of the Los Angeles Olympics, a deranged man drove his car at high speed onto a crowded sidewalk in Westwood Village, California. Westwood Village is immediately adjacent to the Los Angeles campus of the University of California (UCLA). UCLA was one of two designated villages for housing the Olympic athletes, and the streets were particularly busy with pre-Olympic activities.

Triage at the scene was directed by the Los Angeles City Fire Department. Of 51 injured pedestrians, 13 were judged to be in critical conditions. Transportation was arranged for 17 of the 51 (7 critically injured) to the Emergency Medical Center (EMC) of the UCLA Hospital, located two city blocks from the scene. These 17 patients are the basis of this report. The remaining 34 patients (6 critically injured) were transported to four local hospitals (Figure 1). One hospital received ten patients, admitted four (three in critical condition), and released six. Two hospitals received one patient in critical condition and eight noncritically injured patients; one admitted five and the other admitted one. One hospital received six patients, one of whom was critically injured and was the only patient admitted.

Preparing the Trauma Center

Trauma care at the UCLA Medical Center is provided by the Trauma and Emergency Surgery Service. The service is headed by a full-time trauma director (J.R.H.), with resident staffing including a chief resident; two daily inhouse, on-call teams, each consisting of a senior and a junior resident; and a junior resident assigned to the EMC.

In the weeks preceding the Olympics, concern was expressed by law-enforcement personnel that an episode of violence might occur near an Olympic village or venue. To assure an appropriate degree of vigilance and to optimize UCLA's preparedness for such an event during a period of otherwise reduced surgical activity, the trauma director confirmed and documented day-to-day faculty and resident staffing for each surgical service for the months of July and August, including general surgery, pediatric, cardiothoracic, orthopedic, neurosurgery, plastic surgery, head and neck, and urology services. A simple plan was then devised to alert and mobilize these physicians in the event of an incident involving multiple casualties. Features of the plan included the following:

- Contact to be made at the chief resident level, with each chief resident then responsible for mobilizing a team
- Rendezvous at one of two specific points (either the Emergency Medical Center or the operating room) for each team member
- Command at each rendezvous point by a trauma surgery faculty member
- A scheme for admissions to the various services, overseen by the trauma director:

Trauma surgery. All patients with multiple trauma not yet surgically treated; overflow from other services.

Other general surgery services. All patients operated on by them; patients with multisystem trauma after surgical treatment, admitted in rotation.

Cardiothoracic, head and neck, neurosurgery, orthopedics, and urology services. Patients with single-system injuries, with or without operation.

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Plastic surgery. Patients with burns without other injuries; those with isolated major soft tissue injuries without fractures, and those with isolated hand injuries.

Pediatrics. Patients 10 years of age or younger with multisystem injuries.

This "Disaster Plan for the Department of Surgery" did not depend on activating the full hospital disaster plan and was therefore believed to be applicable to a smaller number of severely injured patients. It was published and circulated by the chair of the Department of Surgery a week before the opening of the Olympics.

Trauma Center Response

Following the event on the evening of July 27, notification of the impending transport of multiple casualties preceded the arrival of all but one by about 20 minutes (the first patient was a child carried in by police almost immediately after the accident). During this interval, it was possible to summon most of the Emergency Medical Center faculty back to the hospital. On-call members of the Trauma Surgery Service were alerted and were present in the EMC when the first patient arrived. According to the plan described above, residents and faculty of the general surgery, orthopedic, and neurosurgery services were also summoned to the Center by the Trauma Surgery Service. Some additional surgical faculty and residents reported to the EMC or operating room when they heard the incident broadcast over radio or television. Some had been on the street when the event occurred and either assisted at the scene or accompanied victims to the hospital.

All patients were initially resuscitated by the EMC staff. Evaluation of 11 of the 17 patients was supervised by an EMC faculty physician and of 6 by a senior resident. All patients were also seen by the staff of the Trauma Surgery Service.

Patients and Results

Paramedical personnel transported 12 patients to UCLA during the first hour following the event, and 5 patients presented themselves or were brought in by family members in the ensuing two hours; 12 were female and 5 male, with an average age of 21 years (range 3 to 46). One of the first 12 patients and all of the subsequent 5 had minor cuts and bruises or hysteria and were discharged to the care of a family member; these patients will not be discussed further.

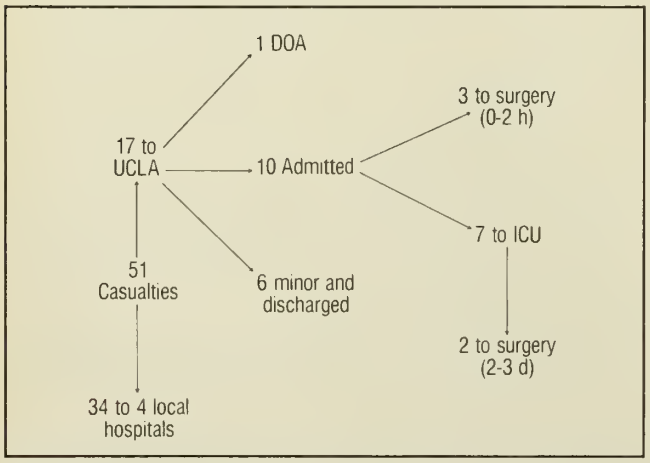

Figure 1.—The flow of patients is shown following a mass traumatic event to 51 persons. DOA = dead on arrival, ICU = intensive care unit

One patient died as a result of the attack. A 20-year-old woman had no vital signs in the field and was transported to the Center following intubation with cardiopulmonary resuscitation in progress. This was continued in the EMC, but she could not be revived.

The mean "injury severity score"[1] of the ten patients who were admitted to the hospital was 13.6 (range 3 to 48). Nine patients had major long bone, vertebral, or pelvic fractures, eight had head or maxillofacial injuries, and one had major chest and abdominal injuries. This last patient was a 22-year-old woman brought to the EMC with a systolic blood pressure of 60 mm of mercury and a distended abdomen. An endotracheal tube was introduced, intravenous lines were placed, and she was taken to the operating room. Her injuries included a ruptured spleen, a traumatic amputation below the right knee, a pelvic fracture, multiple rib fractures with a pulmonary contusion, and a fracture dislocation of the thoracic spine with paraplegia.

Diagnostic procedures done on the remaining nine patients included peritoneal lavage in three (none showing abnormalities) and computed tomography of the head in three (abnormal in one). Resuscitative procedures included endotracheal intubation and a saphenous vein cutdown in one patient each. Two patients required suture of lacerations in the EMC.

Surgical consultants saw eight patients, four were seen by orthopedists, four by neurosurgeons, two by plastic surgeons, and one by head and neck physicians. Four patients were admitted to the trauma surgery service, four to orthopedics, and one each to neurosurgery and pediatric intensive care.

Operations were done on five patients. Two of these were delayed orthopedic procedures carried out two to four days after the incident. Three patients required operations on the night of admission. These included a splenectomy, amputation, and spinal fixation in the patient described above, a craniectomy for treatment of a severe, open-skull fracture in a 3-year-old child, and fixation of a humeral fracture and closure of extremity wounds in a 22-year-old. Three operating rooms were run simultaneously for these procedures.

Two patients required a total of 14 units of blood immediately. The woman with the traumatic amputation needed 13 of these, 4 type-specific, and the remainder crossmatched. The child with an open-skull fracture received half of an adult unit of type O blood at the beginning of resuscitation. Blood was crossmatched for the remaining seriously injured patients but was not administered.

Residual neurologic disabilities in these two patients who required transfusions accounted for the only significant morbidity. There was no inhospital mortality at UCLA or any other center, the only death being the traumatic full arrest described above. Some staff members, including physicians who had witnessed the incident, received psychological post-crisis counseling in the subsequent weeks.

Discussion

Anticipating events that produce mass casualties, managing an extraordinary number of injured patients, and analyzing the characteristics of the event and the quality of the response are among the important functions of a trauma center. Such events are commonly termed "disasters,"[2] and it has been recognized that disasters may be natural or unnatural,[3,4] vary widely in magnitude,[5] and by their analysis ex-

pand knowledge in areas of socioeconomic planning, the pathophysiology of injury, and trauma management.

The Boston Cocoanut Grove fire of 1942 claimed 491 lives and remains an enormous disaster by any standard. The landmark 1943 review of the eare of the victims in the Massachusetts General Hospital[6] revolutionized the knowledge of burn physiology and therapy and demonstrated the successful exeeution of every important function of a modern trauma facility in a fashion that would be admired today. In reports of more recent ineidents, certain of these elements have been serutinized in greater detail. A review of the Las Vegas MGM Grand Hotel fire eonsidered problems of triage of mass casualties from large erowds.[7] The analysis of a bus crash in northern California identified problems that contributed to the cause of the accident and described the important aspects of the rescue effort.[8]

The development of trauma systems has been recognized as a erucial aspect of disaster management that ean distribute the burden of eare to a group of hospitals,[9] as oeeurred in response to the Kansas City Hyatt Regency skywalk eollapse.[10] Problems at the level of the trauma system are being studied,[11] and the present report endeavors to identify the important issues in an individual trauma hospital. Certain principles seem evident.

First, some events invite trouble. One might anticipate an inereased trauma volume during Mardi Gras[12] or the Olympics, with the potential for a larger-scale incident of the sort deseribed in this report. Hospitals have been urged to devise internal plans for response to sueh ineidents.[13,14] The magnitude of the Westwood incident did not justify activating the hospitalwide disaster plan. We found our departmental plan to have been useful, perhaps prineipally because it brought the possibility of such an event to the attention of every surgeon shortly before the Olympics. Interestingly, with the exeeption of the event described in this report, the Olympies provided two very tranquil weeks to Los Angeles hospitals.

Seeond, the importance of a dedieated trauma service was emphasized. The role of such a service in a university has been reviewed by Baker and eo-workers[15]: benefits include standardized trauma care, more available surgieal eonsultation, improved resident edueation, and a reduetion in early and late trauma mortality. In the present instance, a group of general surgeons fully aequainted with the workings of the emergency department and able to interact cordially with Emergeney Medical Center staff was available to direet the evaluation and triage of every patient. Resuscitation was ably accomplished by the EMC faculty and residents; the surgical team's function was to coordinate the optimal deployment of the surgical work force in general surgery and the specialties, and ultimately the trauma team managed the hospital care of most of the patients.

Finally, it was obvious that the ehallenges provided to the hospital by this act of violence were entirely a function of its mechanism. This was an episode of purely blunt trauma, and the victims exhibited all the eharacteristics of blunt injury with which trauma surgeons are familiar. There was a broad range of injury severity, many injuries were minor, most patients were seen by several consultants, and the prineipal challenges were diagnostie, with only 3 of 17 patients requiring operations acutely. The response needed for 17 vietims of penetrating trauma would have been entirely different, and the availability of operating rooms might have been the greatest ehallenge.

The prevalence of urban violence in eontemporary soeiety is a eontinuing justification for organized trauma systems and dedicated eenters. Preparedness for disasters of all types and sizes will yield the best results with these diffieult problems.

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Thoughts on Physician-Assisted Suicide

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We live in a society where the average person is unfamiliar and uncomfortable with death. Beginning with what many psychologists think is an innate block to realizing our own mortality, we go on to shield ourselves in every way possible from the occurrence of death. People die in institutions rather than in the home, and the opportunity to spend time with the dead person at the time of death and perhaps at the funeral home later are quite abbreviated compared to the days-long vigils over the dead of other times and other societies. Our culture emphasizes youth and shuns and ignores the aged, as if to banish from our minds the deterioration and demise for which we all are bound.

Many, if not most, people have never been present at the death of another. Certainly, as we get older and our friends and relatives die, the truth becomes more evident, but we are so conditioned to denial that the truth often is hard indeed to accept.

Into this setting come two organizations: the Hemlock Society and Americans Against Human Suffering. In euphemistic terms they call for "the right to self-deliverance," "voluntary active euthanasia," and "assisted suicide." In the boldest, clearest possible terms, what they seek is legalized mercy killing. The Americans Against Human Suffering organization is gathering signatures for a ballot initiative—the so-called Humane and Dignified Death Act (California Civil Code, Title 10.5*)—that would make physician intervention to cause the death of a consenting, terminally ill patient a legally protected activity in the state of California. If its sponsors are successful, the act will be submitted to the voters in the form of a referendum.

Under the terms of the proposed initiative, any person certified by two physicians as being terminally ill and unlikely to live longer than six months would be entitled, upon the execution of a simple document, with witnesses, to immediate assistance from his or her physician in committing suicide. This would involve anything from writing a prescription for a lethal drug to "any medical procedure that will terminate the life of the qualified patient swiftly, painlessly, and humanely." The physician and any who help in this task would be immune from criminal, civil, or administrative liability. Any physician refusing to assist in the killing would be required to make arrangements for the transfer of the patient's care to another, more willing physician.

In his book, *Let Me Die Before I Wake,* Humphrey makes the case for this legislation simply, poignantly, and persuasively.[1] His argument is primarily one for patient autonomy and personal sovereignty. A terminally ill patient, he says, should have the right to choose the time and circumstances of his or her death. The patient should not have to suffer through a mental or physical decline, emotional and/or physical pain, and the additional expense of treatment if he or she does not want to. If there is no hope, why prolong suffering needlessly?

Patients in this position currently face a number of barriers to "self-deliverance." First, their behavior is legally and socially unsanctioned, so they must make their preparations furtively. Second, the most effective drugs for committing suicide are available only by prescription. People are, therefore, forced to go to great lengths to accumulate a lethal hoard of pharmaceuticals, and in many cases may have to use slower, less certain, and less comfortable drugs or choose other methods of suicide. Third, and perhaps most compelling, is the question of what happens to people who are physically or mentally unable to accomplish their own suicides and know no compassionate souls who will risk helping them. Are they to be abandoned to slow, lingering, painful, undignified, and expensive deaths?

In a series of case histories, Humphrey tells the stories of terminally ill people who accomplish suicide with the help of spouses, children, and friends. In each case the person dies happier, the friends and relatives feel good about their participation, and the last hours spent together are filled with a sense of love, serenity, and even triumph. Why not let all people who choose to die in this way do so without hindrance?

The answer to this question has less to do, I think, with how and when we let people die than it does with how and when we let people kill. Certainly, in my opinion, people who make up their minds to kill themselves have the moral right to do so. They may be considered foolish. They may be called inconsiderate to inflict emotional pain on those who value their lives and will mourn their passing. I think that it is their lives, and so long as they are discreet in choosing the time and method of suicide and attentive to the details, they should not have a problem. The real difficulty begins when they want someone to help them.

We live in a polis that rigidly limits the conditions under which one person may kill or help to kill another. Soldiers are allowed to kill enemies during military confrontations. Police and civilians are allowed to kill in self-defense. Certain criminals may be put to death as punishment for their crimes. All of these cases involve people whose lives have been devalued by virtue of their assuming evil roles relative to the commonweal. While a physician is permitted to hasten a patient's

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(Demac AR: Thoughts on physician-assisted suicide. West J Med 1988 Feb; 148:228-230)

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death by giving morphine, the killing is a by-product of pain relief rather than a stated goal.

The proposed legislation would therefore extend government's role in a significant new direction. It would be given the power and the responsibility to kill the "good guys," people who have not hurt anyone but have devalued their own lives based on their personal views of their lives and circumstances. What are the justifications, limitations, and dangers of such an expansion of power?

The Hemlock Society says that terminally ill people should not have to suffer, but why should anyone have to suffer? Suffering exists and abounds, not simply among the terminally ill. Should anyone who suffers be entitled to help in committing suicide? A possible response is that terminally ill people are unique in that they have no hope. Others have the possibility of relief, of a life after the suffering, but the terminally ill do not. It may, therefore, be argued that there is no reason to force the terminally ill to suffer through as long a period as six months before they finally die and are released.

There are, however, many who suffer great physical pain without hope of relief. For example, the severely handicapped or the severely and chronically ill have to suffer, with no prognosis for improvement. If the terminally ill should not be forced to suffer for six months, why should these people be forced to suffer for years? More to the point, what is the nature of this suffering? Under the proposed initiative, a person would be entitled to assisted death from the moment of being diagnosed as being six months from death, even if no significant deterioration or pain had yet occurred. A terminally ill patient, then, with little physical pain could demand help in committing suicide while a chronically handicapped but not terminally ill person with much more severe pain could not. It is, therefore, impossible to argue that the terminally ill suffer uniquely or are uniquely entitled to a particular form of relief. We must either refuse to grant them assisted suicide on demand or extend the right to others as well.

An important question to ask at this juncture is whether suicide is the only possible solution to the suffering of a terminally ill person. Many believe that it is not. If significant pain does exist, there is no reason why it cannot be palliated by the armamentarium of pain relievers, including morphine and neurosurgery, that are available. If pain is so terrible that death can provide the only relief, it is generally and increasingly recognized that physicians may increase the dosage of morphine until death is in fact effected. This is something the patients can discuss with their physicians in advance, so that they may be assured that they will not suffer unduly.

The Hemlock Society maintains that the terminally ill should not have to suffer the emotional distress and indignity of physical and mental deterioration and increasing dependence on others. Quality of life, however, is entirely subjective, and the hospice movement has shown that even severely debilitated patients can lead meaningful lives. The loss of youth and vitality is eventually suffered by everyone, if they live long enough. As Dyck has pointed out:

> If minimizing suffering is linked with killing, we have the unfortunate implication that killing is a quicker, more painless way to alleviate suffering than is the provision of companionship for the lonely and long-term care for those who are either dying or recuperating from illnesses.[2]

The Hemlock Society further states that terminally ill people should not have to receive pointless, expensive, life-prolonging treatment. This is certainly justified, and as living wills and the right to refuse treatment become institutionalized, as they increasingly are, this will not be a problem. Termination of treatment issues, however, should not be confused with termination of life by "assisted suicide."

While it is difficult for me to understand why death by mercy killing is necessary to ease the departure of a terminally ill person, I see a number of dangers inherent in its legalization. First and foremost, it is quite possible that a social and psychological climate would be created under which terminally ill people would be *expected* to exercise this option. A large amount of money, including a major portion of Medicare payments, is now spent on the care of the terminally ill and could instead be used for other things. Governor Richard Lamm of Colorado has spoken of the duty of the elderly to die. It would be easy for this attitude to be spread in the media to the point where it might act as a pressure on the terminally ill to opt for death by mercy killing. Families and physicians caring for the terminally ill might well be tempted to urge this option on a person to save themselves from the strain of such care.

Furthermore, because, as previously discussed, there is nothing qualitatively unique about the suffering of the terminally ill, it is likely that the right to death by mercy killing and the pressure to take that option would soon be extended to all chronically ill, elderly, and handicapped people. In fact, the underlying assumption of The Humane and Dignified Death Act, which is that poor quality of life is a justification for death, would put society on a slippery slope with no bottom in sight. It is easy to envision a time, especially during an economic depression or a war, when resources are scarce and anyone would be entitled to assisted suicide simply because they were dissatisfied with the quality of their lives. During such a time, a "reasonable person" rule might be applied to those not able to make a choice—the insane, the mentally retarded, or handicapped children—who might be put to death without having any say in the matter on the basis of their relatively poor quality of life.

A final question relating to assisted suicide is who should do the assisting. The Humane and Dignified Death Act calls for physicians to assume this role, but should they? Just as physicians do not participate in executions, they need not be involved in mercy killing. There could be certified thanatologists, or euthanasia societies could establish right-to-die clinics. If physicians are the killers, it arguably could effect a great change in their image and role. Certainly, if assisted suicide becomes a treatment option, all physicians will be required to mention it to their patients or be liable for not keeping their patients properly informed. The proposed legislation requires that a physician opposed to killing a patient must find that patient a physician who will. In this way the physician's complicity is coerced, and proper medical conduct is defined by those outside the profession. On the other hand, in this age of commercial medicine, one can readily imagine physicians competing with one another through advertisements on the basis of their euthanasia services. The image of physicians would thus change from being champions of life to angels of death.

The problem with laws is that often they provide a sledgehammer where a feather is needed. It is widely noted that there are instances when physicians have actively helped patients to die. The impulse is to enshrine this practice in law so that any patient may receive such help and no physician need fear a penalty for providing it. The problem is that this would make the practice easier and more commonplace than it

should be and leave society open to the undesirable consequences mentioned.

A more sensible middle ground has been taken in the Netherlands. While they have not legalized physician-assisted suicide, authorities in that country have worked with the Royal Dutch Medical Association to determine criteria under which physicians may be permitted to help terminally ill patients to die. These include the stipulation that euthanasia will be carried out only if there is unbearable suffering that fails all pain-killing efforts. The goal, according to one Dutch practitioner, is to "prevent the deed's arising from mere subjective despair in an exhausted patient or from a doctor's proselytizing" (*The New York Times,* October 31, 1986, p A4). Implicit is that such a decision should be arrived at by a physician and patient in the context of a long-standing and intimate physician-patient relationship. It is not a decision to be arrived at casually or between physicians and patients who are strangers to one another. Furthermore, cooperation by a physician or other party in such an act should not be coerced in any way.

While suicide in the face of death may be a dramatic assertion of self-determination and the legalization of such practice an affirmation of personal autonomy, we as a society are not ready for such a big step. At this time, we should move forward carefully, allowing the courts, the medical profession, and the public to monitor the situation as we go. The worst thing we could do is to pass a referendum whose provisions would be clumsily broad, and which, by the very nature of referendums, would be difficult to amend as its flaws became apparent.

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AIDS in Children

WHAT ABOUT PRECAUTIONS? In the hospital, this is how we deal with things: We put up our sign, which is the same sign that we use for hepatitis B precautions; obviously, it doesn't say anything about AIDS or HIV. It's called "blood and needle precautions": Children with opportunistic infections, children with chronic generalized lymphadenopathy, failure to thrive, who might be in a high-risk group, and children, obviously, with possible AIDS.

In general, we try to group them together or put them in a single room, both in order to keep them away from other patients (so they don't get infected with RSV and all those other things that go around our ward) but also for obvious reasons. Contaminated linen and all specimens should clearly have a biohazard warning.

The precautions that we take are the same as those we use for hepatitis B. We use gloves if we're going to be in contact with secretions or blood. We use gowns, once again, if we're going to be in direct contact with those things.

Surfaces should be decontaminated. The people who tend to use goggles are the gastroenterologists who are doing procedures on these patients. Generally speaking, we don't use either masks or goggles when we're dealing with these children.

Now, what about at home? Probably the most difficult problem that I have is dealing with the child in the first year of its life, when you don't know what's going on. Later on, when you know a child is infected, it's much easier to talk to parents. If I don't know the child is infected, what I say is that if the mother has any problem with her hands, why, I have her get disposable gloves and use those for any diaper change. Clearly, you want to use extreme care with blood. The parents should wear gloves when they're dealing with any cuts and take care to disinfect.

—KENNETH McINTOSH, MD

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The Duty to Protect Others From Your Patients—*Tarasoff* Spreads to the Northwest

JOSEPH D. BLOOM, MD, *and* JEFFREY L. ROGERS, JD, *Portland*

The California Supreme Court's Tarasoff *decision was the seminal case in the area of the duty to protect third parties from the potential of violence from patients.* Tarasoff*-related issues have now spread to many jurisdictions in the country. This article will pay particular attention to the cases influencing law in Washington and Oregon and will review the clinical duty to protect others from your patients that existed before* Tarasoff, *as physicians were taught to work between privilege and civil commitment statutes. The California law designed to limit* Tarasoff *liability and the reasons why legislators should be willing to support such legislation are discussed.*

(Bloom JD, Rogers JL: The duty to protect others from your patients—*Tarasoff* spreads to the Northwest. West J Med 1988 Feb; 148:231-234)

In 1974 and 1976 the California Supreme Court handed down landmark decisions in the *Tarasoff* case.[1,2] The court's 1974 opinion enunciated a legal duty for psychotherapists to warn possible victims of their patients' potentially violent acts. This decision produced significant turmoil in the mental health community. At the request of many professional organizations, the court agreed to reconsider its decision. Instead of abandoning the previously adopted duty to warn, however, the court's 1976 opinion expanded the action required of psychotherapists to include "whatever other steps are reasonably necessary under the circumstances." The duty to warn third parties was thus expanded into a more clinically relevant but broader duty to take preventive action or, as it is now being called, "the duty to protect." In this article we will first look at what clinicians were taught before *Tarasoff.* This will be followed by a discussion of the three major cases that influence clinical practice in Washington and Oregon. We will conclude with a discussion of the legislative steps now being taken in an attempt to limit liability in this difficult area.

Pre-Tarasoff Issues

One of us (J.D.B.) began psychiatric training in 1963. In the first weeks of training we learned that psychiatrists were to respect patients' confidential communications. At the same time, we were expected to act when we thought that a patient was either suicidal or homicidal. We gave this message to patients: What you tell me is confidential; however, if I decide that you are dangerous to yourself or to someone else, I am going to have to take action to prevent harm to you or to these persons. We had adopted a clinical duty to protect based on our assessment of what was primarily in the patient's and, only secondarily, in the community's best interests. Psychiatrists were taught to operate within a narrow legal framework defined by the statutes of privilege and civil commitment: one prohibited disclosure and the other allowed psychiatrists to reveal information in specific situations.

This legal framework still exists. Current Oregon statutes illustrate, on one hand, the strongly worded psychotherapist-patient privilege:

> A patient has a privilege to refuse to disclose and to prevent any other person from disclosing confidential communications made for the purposes of diagnosis or treatment of the patient's mental or emotional condition among the patient, the patient's psychotherapist, or persons who are participating in the diagnosis or treatment under the direction of the psychotherapist, including members of the patient's family.[3]

The importance of confidentiality to the practice of medicine can be further illustrated by the Oregon Medical Practice Act. One of the grounds for suspending, revoking, or refusing to grant a medical license is "divulging a professional secret."[4] This statute reflects the long history of the importance of confidentiality in the doctor-patient relationship, which is deeply ingrained in the professional practice and ethics of medicine.

Civil commitment, on the other hand, allows physicians to admit mentally disordered patients to hospitals when a person is potentially dangerous to self or unable to care for his or her needs in the community. As defined in Oregon statute:

> "Mentally ill person" means a person who, because of a mental disorder, is either:
>
> (a) Dangerous to self or others; or
>
> (b) Unable to provide for basic personal needs and is not receiving such care as is necessary for health or safety.[2]

Before the *Tarasoff* decision, then, clinicians operated in a system in which it was necessary to steer a course between respecting or revealing a patient's disclosures based on a model that was concerned primarily with the protection of the patient. There existed a clinical duty to protect. The following is a discussion of actions before the creation of a legal duty to protect.

Case Example

One of the authors (J.D.B.) held a regularly scheduled psychiatric clinic in a rural town. The clinic was coordinated

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ABBREVIATIONS USED IN TEXT

PSRB = Psychiatric Security Review Board
VA = Veterans Administration

by the local family practitioner, who did a fair amount of counseling on his own and scheduled the difficult psychiatric consultation questions and the severely mentally ill patients for the psychiatrist. During one visit he referred a teenaged boy who was having school discipline problems. The administration at the local high school had recently changed, and the school had become more conservative and discipline-oriented. This young man was very angry at the new school authorities and was in constant trouble with them.

When seen by the psychiatrist, the young man was indeed very angry. He felt that his school had betrayed him and that his views were shared by other students. In addition, he had decided to do something about the problem. His father kept some dynamite at home and had taught him how to use it. He said that in the next few weeks he planned to dynamite the school at night when everyone had left the building. He stated that he was determined to carry out his plan. The psychiatrist and the family physician discussed the case and told the patient that we had to try to stop him from doing something that might injure someone and/or might ruin the patient's life. He was very angry when told that we needed to see him with his parents so that they would know what was going on.

A family conference was scheduled with the young man, his parents, the family practitioner, and the psychiatrist. The young man was asked to tell his parents about his problems at school and then to tell them what he intended to do about it. His mother became greatly agitated; his father was quietly thoughtful while his son told him he was going to blow up the school with the dynamite from the family tool shed. After considering the story for a long time, the father said, "Well, I think he can do it; he sure knows how to use dynamite. I guess I am going to have to take it away from him." The patient was seen individually after the family conference. He was now very angry at the physicians but continued to want to talk. On subsequent visits, his anger toward the school gradually subsided. Therapy was terminated and the school remained intact; no one at the school was ever informed of the threat.

The case was frightening then and is even more so now, given the *Tarasoff* decision. What would we do in a case like this now? Was the right thing done then?

The Tarasoff Decision and the Northwest Cases

The *Tarasoff* case flies in the face of the tradition of medicine just reviewed, where cases were handled, for the most part, by physicians and hospitals. *Tarasoff* broke new legal ground. The facts of the *Tarasoff* case have been described on numerous occasions.[7] The drastic change in medical tradition was justified by the California Supreme Court by a very stark view of the dangers of modern society.

> Our current crowded and computerized society compels the interdependence of its members. In this risk-infested society we can hardly tolerate the further exposure to danger that would result from a concealed knowledge of the therapist that his patient was lethal. If the exercise of reasonable care to protect the threatened victim requires the therapist to warn the endangered party or those who can reasonably be expected to notify him, we see no sufficient societal interest that would protect and justify concealment. The containment of such risks lies in the public interest.[1]

Three subsequent cases, all derivatives of the *Tarasoff* decision, currently influence law and medical practice in Washington and Oregon. The first is a California case from the Ninth Circuit Federal Court of Appeals, followed by cases from the Washington and Oregon Supreme Courts. Each will be reviewed briefly.

Jablonski v United States.[8] The plaintiff, Megan Jablonski, brought suit against the Veterans Administration (VA) for the wrongful death of her mother, Melinda Kimball, who was killed by the man she was living with, Phillip Jablonski. In July 1978 Phillip Jablonski had threatened Ms Jablonski's mother and had attempted to rape her. The mother decided not to file charges but attempted to have the police enter Jablonski into psychiatric treatment. The police called the nearby VA Medical Center and were told that Jablonski would be evaluated by a certain physician. The police spoke with another psychiatrist and advised him of Jablonski's prior criminal record and indicated that they believed Jablonski warranted inpatient treatment. The physician indicated that he would transmit this information to the evaluating psychiatrist but failed to do so.

Several days later Jablonski was evaluated at the VA Medical Center. During the examination the psychiatrist did learn that Jablonski had served a five-year sentence for raping his ex-wife and that four days earlier he had attempted to rape the plaintiff's mother. Jablonski indicated that he had undergone previous psychiatric treatment but refused to say where. Voluntary admission to hospital was recommended. When the patient refused, a return appointment was set. The psychiatrist's note indicated that he perceived Jablonski as dangerous but not civilly commitable.

Following the interview Ms Kimball and the psychiatrist met. She indicated to the psychiatrist that she was concerned about Jablonski's behavior, and the psychiatrist suggested that she leave him, at least during this time. No attempt was made to locate the prior medical records that would have indicated that Jablonski had homicidal ideation in the past and predicted future violent acts. Jablonski was seen again as an outpatient four or five days later. He still was perceived to be potentially dangerous, and his next appointment was scheduled for three days later. On the day before that next appointment, Ms Kimball went to Jablonski's apartment and, while there, was murdered.

The Federal District Court found the psychiatrists to be negligent in this case for failing to record and transmit the police department's recommendation, in failing to obtain medical records, and in failing to adequately warn the victim. The Veterans Administration appealed. The Ninth Circuit Court of Appeals affirmed the trial court's decision. It reasoned that the psychiatrists had a duty to protect Ms Kimball. The court found sufficient evidence that the physicians breached their duty in all three ways identified by the trial judge. The court thought that if these three negligent failures had not occurred, action could have been taken to prevent the killing.

The VA hospital argued that physicians had no duty to protect Ms Kimball, as the patient had not specifically said he would harm her, and that she was not sufficiently targeted as a victim. The court rejected this argument, finding that lack of a specific threat was immaterial because Jablonski's past history indicated that he would likely direct his violence against Ms Kimball.

Although this was a California case, it was the first *Tarasoff*-type case decided by a court with jurisdiction in the Northwest—the Ninth Federal Circuit includes Oregon and

Washington as well as California and several other western states.

Petersen v State of Washington.[9] On May 14, 1977, the plaintiff, Cynthia Petersen, was injured in an automobile accident in Tacoma, Washington. While making a lawful turn at an intersection, she was struck by a vehicle driven by Larry Knox after he ran a red light while traveling at more than 50 miles per hour. Witnesses said Knox was under the influence of drugs. At the time of the accident, he was on probation for a 1975 burglary for which he had been given a 15-year suspended sentence on the condition that he participate in mental health counseling and refrain from drug use.

Five days before the accident he had been released from a Washington state hospital, where he had been admitted to hospital under Washington's civil commitment statute. A month earlier he had cut out his left testicle. While in the hospital, he was treated with neuroleptic medication. Just before his discharge, he was allowed to go home on a pass and was required to return that evening to the hospital. On his return from his pass he was found driving recklessly on the hospital grounds by security personnel. He was still released the following morning with a discharge diagnosis of a schizophrenic-like reaction due to drug use. He was thought to be in contact with reality and back to his "usual personality and behavior." Five days later the accident occurred. It was later learned that he had discontinued taking his medications after discharge from the hospital. Some time after the accident, Knox raped a woman and murdered both of her parents. At that time he was examined by two psychiatrists, who said that he was schizophrenic. This evidence was admitted into the Petersen trial bearing on the question of his diagnosis.

The Washington State Supreme Court, in upholding the decision for the plaintiff, not only adopted a *Tarasoff* standard but expanded it to include potential victims who could not be identified in advance. It held that the doctor "incurred a duty to take reasonable precautions to protect anyone who might foreseeably be injured by [the patient's] drug-related mental problems."

Cain v Rijken.[10,11] This case was brought by the personal representative of the decedent, who was killed in an automobile accident involving the defendant, Paul Rijken. At the time of the accident, Rijken was on conditional release to a day-treatment program in Portland and was under the supervision of the Oregon Psychiatric Security Review Board (PSRB). He had been found not guilty by reason of insanity on a prior charge and was placed under the jurisdiction of the PSRB,[12] which had put him in a monitored conditional release program in a community hospital operated by the PSRB.[13] While under that jurisdiction, Rijken had operated a motor vehicle in a reckless manner, speeding through an intersection and causing the accident that resulted in the death of the plaintiff. The trial court had granted a motion for summary judgment in favor of the mental health program, and, on appeal, the case focused on the issue of whether or not this program owed a duty to the plaintiff.

The court of appeals reversed the summary judgment and remanded the case for trial. Their ruling was based on several important factors. One was that the statute governing the Oregon PSRB makes it very clear that the primary function of the PSRB is to protect society. The second factor was Rijken's past history: Rijken had a diagnosis of schizoaffective psychosis characterized "by periods of manic activity, poor judgment and hallucinations." Several days before the automobile accident, he was reported to be in a deteriorated mental condition. His previous convictions, which had led to his placement under the supervision of the PSRB, included violating traffic laws, failing to remain at the scene of an accident, and attempting to elude arrest. Further background information included a longer history of misuse of his automobile, including previous traffic offenses. The appeals court stated that the program "knew that an earlier psychotic episode had resulted in Rijken driving recklessly and that Rijken's symptoms shortly before he caused the plaintiff's death indicated that his disease had become or was becoming active and was rendering him potentially dangerous to those of the class that the plaintiff was a member," namely, the driving public.

The Oregon Supreme Court affirmed the court of appeals' reversal of the summary judgment, holding that the hospital had a duty of reasonable care in treating patients and controlling their acts, that a breach of that duty creates potential liability to persons who are foreseeably endangered, and that a jury should be asked to decide if the risk to members of the public not specifically identifiable in advance was foreseeable in these circumstances. The court concluded that this case did not involve traditional negligence doctrines; rather, the duty to protect others was created by the Oregon Psychiatric Security Review Board statutes, which require protection of society. The court pointed out that its decision was not based on the *Tarasoff* doctrine. Nonetheless, although the legal doctrines have distinguishable bases, the practical effect for psychotherapists may be comparable, and the decision fits within the growing body of law developed following the *Tarasoff* decision.

The *Jablonski, Petersen,* and *Rijken* decisions extended the original *Tarasoff* doctrine in various ways. The *Jablonski* decision went beyond warning to the protection of identifiable victims, even when the victim already knew about the threat. In the *Petersen* case, a treating facility was found liable and, in *Rijken,* potentially liable for not taking the action necessary to protect foreseeable classes of victims even if no specific victim could be identified in advance. Both also extended the *Tarasoff* doctrine into the area of motor vehicle regulation. A recent article by Stone[14] described the extension of *Tarasoff* into the area of property damage. Notwithstanding the few cases that place confidentiality paramount to protecting third parties, it is clear that the *Tarasoff* doctrine is spreading.

Limiting the Scope of the Tarasoff Doctrine

Most recently we have seen the *Tarasoff* arena shift from the courts to the state legislatures. California's legislature became the first to pass a duty-to-protect statute[15]:

(a) There shall be no monetary liability on the part of, and no cause of action shall arise against, any person who is a psychotherapist as defined in Section 1010 of the Evidence Code in failing to warn of and protect from a patient's threatened violent behavior or failing to predict and warn of and protect from a patient's violent behavior except where the patient has communicated to the psychotherapist a serious threat of physical violence against a reasonably identifiable victim or victims.

(b) If there is a duty to warn and protect under the limited circumstances specified above, the duty shall be discharged by the psychotherapist making reasonable efforts to communicate the threat to the victim or victims and to a law enforcement agency.

This statute attempts to limit liability to circumstances where there is a threat of violent behavior communicated to the psychotherapist against an identifiable victim or victims. The statute provides for discharge of the duty of the therapist

by his or her making a reasonable effort to communicate the threat to the potential victim or to a law enforcement agency. Bills similar to California's statute have recently been introduced into legislation in other states. Some of these go further by allowing discharge of the duty to be accomplished by the initiation of civil commitment. Some also add an additional statement exempting actions taken under these statutes from being considered as breaches of privilege.

It should be made clear that the duty to warn potential victims as described in the *Tarasoff* doctrine is separate and distinct from a clinical duty a physician may have to alert his or her patient to possible dangers inherent in a patient's medical condition. For example, conditions that affect a person's capacity to drive should be discussed with the patient, and, in some jurisdictions, reporting of such conditions is being required by statute and case law.

Although concerns are already being expressed about the value of statutes that attempt to limit *Tarasoff* liability,[16] there are powerful arguments that can be made to legislative bodies for limiting *Tarasoff*. There remains great respect for the protection of confidentiality and of privileged communications. Society benefits from such protections, and many legislators have supported strong privilege statutes.

There is also the ever-present quandary surrounding the prediction of dangerousness. Clear evidence exists of the inability of psychiatrists to predict long-term dangerousness.[17,18] The attack on the prediction of dangerousness has become more acute with the revitalization of death penalty statutes. It is now generally accepted that psychiatrists should not be making such predictions in forensic settings, and, by extrapolation, it seems logical to conclude that these predictions cannot be made accurately in office practices. Many legislatures have had to grapple with this problem in relation to other forensic matters, such as the insanity defense, dangerous offender, or death penalty statutes. The same argument can be made at this time for limiting the aspect of prediction in the *Tarasoff* doctrine.

Finally, there is the issue of the treatment of violent and potentially violent individuals. For public policy reasons, legislators should not want to handicap those therapists who are willing and able to undertake the treatment of violence-prone patients by reducing the therapist's inclination to take such persons into treatment.[19] For these reasons we would predict reasonable success for the limitation of the *Tarasoff* decision by state legislatures. The effects of these laws, once they are in place, on clinical practice awaits empiric study.

Conclusion

We have noted the spread of the *Tarasoff* doctrine and described recent cases, each of which added to the original formulation. This melding of the *Tarasoff* doctrine to the area of the dangerous offender brings another new dimension to the *Tarasoff* situation. Generally, insanity acquittees are considered by statutory definition to be dangerous persons. To some degree, so are many persons who have been civilly committed. Outpatient treatment of insanity acquittees and civilly committed patients is an important step forward. Many states are now recognizing the potential benefits of mandated outpatient treatment.

An unlimited *Tarasoff* doctrine is a threat to the development of community treatment resources for those mentally ill patients who are defined by statute as dangerous. Legislative limitation of the *Tarasoff* liability is one important step. Further legal steps such as the granting of statutory immunities may be necessary to nurture the mandated outpatient treatment system. This may become necessary should treatment centers be unwilling to place themselves in situations where liability may be confirmed almost by the very nature of the legal definition of the population they are attempting to serve.

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Preventing Occupational Low-Back Pain

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THE COMPLEX COMPENSATION and disability issues surrounding occupational low-back pain require the maximal use of preventive strategies by occupational medicine practitioners.

The primary prevention of occupational low-back pain involves the following techniques to prevent an injury from occurring:

Training and education efforts have typically been directed toward workers, management, and practitioners who treat occupational low-back pain. Worker training has usually focused on proper work methods and procedures, especially safe lifting techniques. The *Work Practices Guide for Manual Lifting,*[1] published by the National Institute of Occupational Safety and Health, sets forth an objective approach to quantify safe versus unsafe lifting tasks. Variables such as an object's weight, the horizontal distance of the object from the body, the vertical travel distance, and the frequency and duration of lifting are formulated into a numerical "action limit" below which manual lifting would be considered safe for virtually all men and 75% of women. Defined as three times the action limit, the maximal permissible limit is the value above which only 25% of men and virtually no women could be expected to safely lift. Engineering controls are recommended for lifting tasks above this limit. Between the action limit and the maximal permissible limit, administrative or engineering controls are advised to reduce the risk of an overexertion injury. Typical administrative controls might include worker selection criteria, strength and fitness testing, worker training, or rotation schedules to reduce lifting times. Typical engineering controls could include container design and weight, human/container coupling design such as the use of handles, worker-floor coupling design, hoists, conveyors, or robotic devices.

Strength and fitness training has been recommended as a method to reduce or prevent the occurrence of occupational low-back pain. Although there are conflicting data about the effectiveness of strength and fitness training, it appears that the positive evidence outweighs the negative. Physical fitness and aerobic conditioning should be considered as personal health assets in preventing back injuries.

Ergonomically designing a job to match a worker's ability represents a significant strategy in the primary prevention of work-related low-back pain. Redesigning jobs to reduce or eliminate the amount of manual handling has been advocated by ergonomists to reduce the work-related incidence of low-back pain. The *Work Practices Guide for Manual Lifting* and a computerized two-dimensional strength-prediction model developed by the University of Michigan have both been useful in identifying and redesigning high-risk manual handling activities.

Reducing excessive bending, twisting, reaching, heavy loads, prolonged sitting, vibration, and falling through improved job design are additional prevention roles of occupational health and safety practitioners.[2]

Worker selection techniques include an accurate medical history to document preexisting episodes of lost workdays from back pain or back operations. Isometric strength tests that match a worker's strength to job lifting tasks have been promoted as an effective administration tool to prevent occupational low-back pain from manual handling activities.[3] Routine x-ray films of the lumbar spine have not been helpful in predicting future episodes of low-back pain. The small yield cannot be justified in terms of excess cost or unnecessary radiation exposure.

Back schools represent a comprehensive approach to preventive back care. The original concept was to educate patients who were either suffering or had suffered from acute back pain. Recent evidence suggests that back schools are not effective in the primary prevention of occupational low-back pain.

Secondary prevention strategies, by definition, are designed to reduce or prevent complications due to long-term disability after an injury has occurred. Poor recovery results are associated with adversarial management situations, litigation over compensation, hospital admissions, and a lack of follow-up and concern. Early intervention by management, physicians, and insurance adjusters has been shown to be highly successful in reducing complications due to occupational low-back pain.

(Johns RE Jr: Preventing occupational low-back pain. West J Med 1988 Feb; 148:235)

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Book Reviews

DOCTORS OF MEDICINE IN NEW MEXICO: A HISTORY OF HEALTH AND MEDICAL PRACTICE—1886-1986—Jake W. Spidle, Jr, Professor of History, University of New Mexico, Albuquerque. University of New Mexico Press, Albuquerque, NM 87131, 1986. 320 pages, $29.95.

Jake Spidle, Professor of History at the University of New Mexico, has contributed an interesting, well-written account of doctors in New Mexico. The book developed from a centennial (1886-1986) history project of the New Mexico Medical Society. Although it fulfills the memorial aims of the sponsoring organization, Spidle blends the history of the state with the revolutionary changes in the practice of medicine. The hand of a professional historian is revealed by his skillful use of oral histories and a scholarly use of published and unpublished sources.

In the early history of New Mexico, the tuberculosis business was nothing less than coequal in importance to the cattle and mining industries. The high desert air of the region was considered salubrious for tuberculosis. It brought in an army of consumptives seeking the cure, often in the sanatoriums that proliferated for their care. Many of the doctors also were "lungers." By midcentury, tuberculosis was controlled and the sanatorium business perished.

"Las Doctoras," the chapter about women physicians, is particularly intriguing. Small in number but large in their contributions, they were the key movers in reducing the shameful infant and maternal mortality. One of them, Evelyn Frisbie, in 1916 became the first woman president of a state medical society.

Public health was not organized on a statewide basis until 1919, seven years after New Mexico became a state. A malaria eradication program was successfully carried out, with a practitioner, Charles Gerber, as the driving force. A systematic development of the department was initiated by a Public Health Service officer, Clifford Waller, who was assigned to the state. Vital statistics, registration, sanitation, and surveillance programs became routine. These were supported by practitioners and their society. There remained wariness about visiting health nurses and other potential threats to medical practice.

New Mexico entered the modern era of medicine during the 1950s, with the expansion of the Lovelace Medical Center and the opening in 1964 of a four-year school of medicine at the University of New Mexico in Albuquerque. The New Mexico Medical Society was the coordinating instrument for medical standards and other medical affairs.

Missing from the book are the economic aspects of medicine and attempts to achieve cost containment. Missing also, sadly, are discussions of the Indian populations and their health problems. The roles of federal programs in medicine, including the fiascos of Regional Medical Programs and Comprehensive Health Planning, are underplayed.

The book is attractively printed, but many photographs are of poor quality. The book is recommended to medical historians but is of sufficient interest for general readers as well.

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ABDOMINAL ULTRASOUND—Carol A. Mittelstaedt, MD, Associate Professor, Radiology and Obstetrics and Gynecology, University of North Carolina at Chapel Hill. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1987. 711 pages, $149.

This text contains comprehensive coverage of several aspects of abdominal ultrasound, including imaging of the liver, biliary system, pancreas, urinary tract, retroperitoneum, and peritoneal cavities, abdominal vascular structures, spleen and GI tract. It is fairly easy to read and the layout is excellent. Individual chapters are organized to include discussions of the approach to sonographic imaging of particular structures, normal and abnormal anatomic relationships, and a wide range of pathology. Each chapter closes with a discussion of ultrasound's sensitivity and specificity for imaging various abnormalities, as well as a comparison of diagnostic accuracy between sonography and other imaging techniques. A comprehensive list of reference articles is included. The scans, which include both static and real-time images, are well executed and have been clearly reproduced and annotated.

There are occasional discussions that are repetitious. The chapters on interventional and intraoperative ultrasound are brief and may perhaps leave the uninitiated sonographer ill-equipped to handle many of the problems in these areas. The chapter on vascular ultrasound is grossly lacking in the use of doppler technique in evaluating the abdominal vessels. The section on prostate imaging is limited and incomplete. Obstetric and gynecologic imaging are not covered. To some extent, this limits the book's scope of usefulness with regard to pelvic imaging.

Overall, the text contains valuable and practical information. Neophyte sonographers will benefit from considerable technical and basic details while the experienced radiologist will find practical approaches to imaging that will improve diagnostic skills.

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CURRENT EMERGENCY THERAPY—Third Edition—Edited by Richard F. Edlich, MD, PhD, Distinguished Professor, Plastic Surgery and Biomedical Engineering, and Director, University of Virginia Burn Center, and Daniel A. Spyker, PhD, MD, Assistant Professor of Internal Medicine and Co-Director, Blue Ridge Poison Center, University of Virginia School of Medicine, Charlottesville. Aspen Publishers, Inc, 1600 Research Blvd, Rockville, MD 20850, 1986. 578 pages, $77.

The new edition of *Current Emergency Therapy* exhibits the precise economy of thought and word that busy emergency physicians have come to admire. The publisher has abandoned the "vintage" label (previous editions bore their publication year in the title). The principal authors have maintained an impressive list of contributing authorities who are established "heavy hitters" in their specialties. Approximately 400 pages have been trimmed from the earlier edition. Quality and pertinence of information have not been sacrificed but trimming an inch in girth and three pounds from the weight of this book makes it truly portable and therefore practical.

The first section, or about half the book, is devoted to traumatic injury. It is organized into a true "head-to-toe" format or more specifically skull to digital injury. Throughout this section, there is concentration on trauma known to be troublesome to both rookie and veteran emergency physicians (high pressure injection injuries, compartmental syndromes, foreign bodies, needle sticks, and rabies prophylaxis—to name a few). By contrast, penetrating trauma and acute CNS injury are presented with scant detail. The logic of this is obvious—these serious injuries are promptly referred to appropriate surgical specialists. The "head-to-toe" format should be appreciated by teachers of Advanced Life Support, reinforcing the concept of a systematic approach to assess trauma victims.

The second half of the book covers nontraumatic medical and surgical emergencies. Here is where most of the weight loss took place, compared to earlier editions. Some readers may not appreciate this finely tuned editing of sparse text. To this reviewer, good emergency care dictates referral of hepatitis, hypertension, and heart attacks. If this book lacks detail concerning these problems but elaborates on tetanus, toxicology, and tachycardias, it better serves the emergency physician's needs.

As in previous editions, short bibliographies follow each chapter. These are thoughtfully provided and annotated with a one-sentence summary. The references are timely and should provide a convenient starting point for any reader who seeks more detail on a topic.

Few emergency departments can spare the space for a library-sized dictionary stand, which would be a safe way to keep the earlier editions accessible. Yet, physicians and nurse staff would appreciate this book in their emergency departments to answer the unique questions that arise in emergency practice. A toddler is brought in having gobbled down a fistful of tasty vitamins. Your regional poison center puts you on hold because they are dealing with a more critical case. It's true—Flintstones vitamins contain 50% more iron than Monsters vitamins (p 474). A wheezing fireman sits uncomfortably on the edge of bed #2. What are the toxic elements common to housefire smoke? (p 236). Some data may seem trivial (P.I.D. costs this country $3 billion annually—p 554) but most of the information is pertinent.

If the book appeals to teachers of emergency medicine, it should be attractive to medical students and specialty board candidates who need concise systematic review. They will find it a durable, quality-bound text with an attractively grained leather facade of deep green. Those who dislike dark green covers will appreciate its brightening by slightly gaudy white and gold print and trim. There are few textbooks dedicated to the specialty of emergency medicine and even fewer good ones. We are often forced to rely on classic texts of the traditional specialties to find authoritative information. Despite the publisher's implication by using the word "Current" in the title, this book is more a text than a periodical. It is both too comprehensive and too expensive to attract annual or even biennial buyers. It should, however, prove a well-used addition to any good emergency medicine library.

WILLIAM A. BOEHM, MD
Alamogordo, New Mexico

Check our vital signs.

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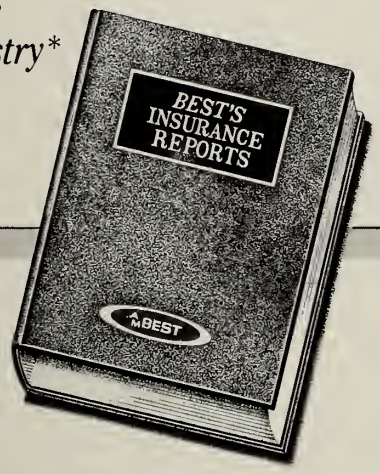

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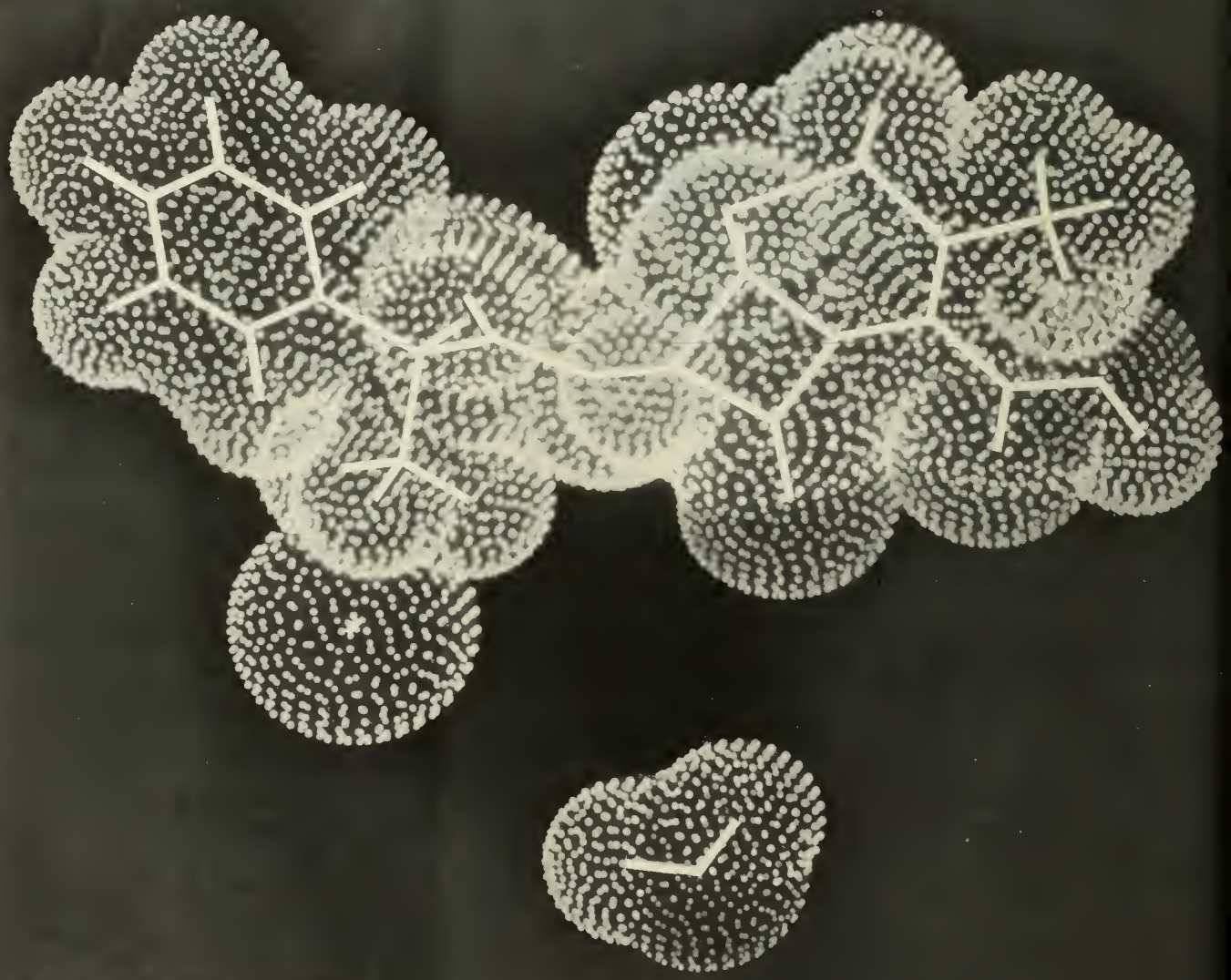

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skin and skin structure infections*
uncomplicated cystitis†
pharyngitis‡

New hydrochloride salt form of cephalexin—requires no conversion in the stomach before absorption

Well-tolerated therapy

May be taken without regard to meals

other indicated infections, 250-mg tablets available q.i.d. dosage

iced less than Keflex®(cephalexin)

ab is contraindicated in patients with known allergy to the halosporins and should be given cautiously to penicillin-sitive patients.

icillin is the drug of choice in the treatment and prevention reptococcal infections, including the prophylaxis eumatic fever.

to susceptible strains of *Staphylococcus aureus* and/or β-hemolytic streptococci.
to susceptible strains of *Escherichia coli*, *Proteus mirabilis*, and *Klebsiella* sp.
to susceptible strains of group A β-hemolytic streptococci.

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(cephalexin hydrochloride monohydrate)

Summary: Consult the package literature for prescribing information.

Indications and Usage:

Respiratory tract infections caused by susceptible strains of *Streptococcus pneumoniae* and group A β-hemolytic streptococci.

Skin and skin structure infections caused by susceptible strains of *Staphylococcus aureus* and/or β-hemolytic streptococci.

Bone infections caused by susceptible strains of *S aureus* and/or *Proteus mirabilis*.

Genitourinary tract infections, including acute prostatitis, caused by susceptible strains of *Escherichia coli*, *P mirabilis*, and *Klebsiella* sp.

Contraindication: Known allergy to cephalosporins.

Warnings: KEFTAB SHOULD BE ADMINISTERED CAUTIOUSLY TO PENICILLIN-SENSITIVE PATIENTS. PENICILLINS AND CEPHALOSPORINS SHOW PARTIAL CROSS-ALLERGENICITY. POSSIBLE REACTIONS INCLUDE ANAPHYLAXIS.

Administer cautiously to allergic patients.

Pseudomembranous colitis has been reported with virtually all broad-spectrum antibiotics. It must be considered in differential diagnosis of antibiotic-associated diarrhea. Colon flora is altered by broad-spectrum antibiotic treatment, possibly resulting in antibiotic-associated colitis.

Precautions:

- Discontinue Keftab in the event of allergic reactions to it.
- Prolonged use may result in overgrowth of nonsusceptible organisms.
- Positive direct Coombs' tests have been reported during treatment with cephalosporins.
- Keftab should be administered cautiously in the presence of markedly impaired renal function. Although dosage adjustments in moderate to severe renal impairment are usually not required, careful clinical observation and laboratory studies should be made.
- Broad-spectrum antibiotics should be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis.
- Safety and effectiveness have not been determined in pregnancy and lactation. Cephalexin is excreted in mother's milk. Exercise caution in prescribing Keftab for these patients.
- Safety and effectiveness in children have not been established.

Adverse Reactions:

- *Gastrointestinal*, including diarrhea and, rarely, nausea and vomiting. Transient hepatitis and cholestatic jaundice have been reported rarely.
- *Hypersensitivity* in the form of rash, urticaria, angioedema, and, rarely, erythema multiforme, Stevens-Johnson syndrome, or toxic epidermal necrolysis.
- *Anaphylaxis* has been reported.
- *Other reactions* have included genital/anal pruritus, genital moniliasis, vaginitis/vaginal discharge, dizziness, fatigue, headache, eosinophilia, neutropenia, and thrombocytopenia; reversible interstitial nephritis has been reported rarely.
- Cephalosporins have been implicated in triggering seizures, particularly in patients with renal impairment.
- *Abnormalities in laboratory test results* included slight elevations in aspartate aminotransferase (AST, SGOT) and alanine aminotransferase (ALT, SGPT). False-positive reactions for glucose in the urine may occur with Benedict's or Fehling's solution and Clinitest® tablets but not with Tes-Tape® (Glucose Enzymatic Test Strip, USP, Lilly).

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CONTINUING MEDICAL EDUCATION

(Continued from Page 158)

March 11-12—**Arrhythmias: Interpretation, Diagnosis and Management.** Medical Education Resources at Tropicana Hotel, Las Vegas, Nevada. Fri-Sat. 11-13 hrs. $225-$295. Contact: MER, 5808 S. Rapp St., Suite 202, Littleton, CO 80120. (800) 421-3756.

March 21-23—**New Directions in Cardiac Rehabilitation.** ACC & Stanford University School of Medicine at Stanford. Mon-Wed. Contact: Registration Secretary EP Dept., ACC, Bethesda, MD (301) 897-5400.

March 25-27—**Coronary Heart Disease: Current Concepts.** Medical Education Resources at Inter-Continental Hotel, Maui, Hawaii. Fri-Sun. 11-13 hrs. $225-$295. Contact: MER, 5808 S. Rapp St., Suite 202, Littleton, CO 80120. (800) 421-3756.

April 15-17—**Coronary Artery Disease: A Commemorative Symposium—75 Years Since Anitschkow and Herrick.** UCSF. Contact: UCSF.

April 18-27—**Cardiology for the Consultant.** Scripps Clinic and Research Foundation at the Inn at Rancho Santa Fe, Rancho Santa Fe. Mon-Wed. 40 hrs. $900. Contact: Bonny Mower, 10666 N. Torrey Pines Road, La Jolla, 92037. (619) 457-8556.

May 7—**Third Annual Cardiology Symposium.** Sutter Health at Sacramento Inn, Sacramento. Sat. 6 hrs. Contact: Sutter Health, CME Dept. 2020 I St, Suite D, Sacramento 95814. (916) 446-7681.

May 13-14—**Coronary Heart Disease: Current Concepts.** Medical Education Resources at Hilton Hotel, San Francisco. Wed-Thur. 11-13 hrs. $225-$295. Contact: MER, 5808 S. Rapp St., Suite 202, Littleton, CO 80120. (800) 421-3756.

May 19-20—**Cardiology for the Non-Cardiologist.** UCI. Thurs-Fri. Contact: UCI.

June 6-8—**Advanced Echocardiography & Doppler Ultrasound 1988.** American College of Cardiology at Sheraton Harbor Island, San Diego. Mon-Wed. Contact: Registration Secretary, EP Dept. ACC, 9111 Old Georgetown Road, Bethesda, MD 20814.

June 30-July 2—**Consultative Cardiology: Update in Diagnostic and Therapeutic Techniques.** ACC, Orange Coast Heart Institute and Hoag Memorial Hospital at Westin South Coast Plaza, Costa Mesa. Thur-Sat. Contact: Registration Secretary, EP Dept., ACC, 9111 Old Georgetown Road, Bethesda, MD 20814.

DERMATOLOGY

February 27—**Summary of Clinical Use of Argon, YAG, CO2 Lasers for Cutaneous Lesions.** Palo Alto Medical Foundation at Palo Alto Medical Clinic. Sat. 6 hrs. Contact: Palo Alto Medical Clinic, 300 Homer Ave, Palo Alto 94301. (415) 321-4121.

May 21—**Summary of Clinical Use of Argon, YAG, and CO2 Lasers for Cutaneous Lesions.** Palo Alto Medical Foundation at Palo Alto Medical Clinic. Sat. 6 hrs. Contact: Palo Alto Medical Clinic, 300 Homer Ave, Palo Alto 94301. (415) 321-4121.

August 12-14—**Dermatologic Surgery: State of the Art 1988.** Stanford University at Monterey Sheraton, Monterey. Fri-Sun. Contact: Paul H. Jacobs, MD, Dept. of Dermatology, UMC Stanford, 94305. (415) 723-6105.

August 21-28—**International Symposium: Hot Spots in Dermatology.** Kauai Medical Group at Molokai, Hawaii. One week. Contact: David Elpern, MD, 3420-B Kuhio Highway, Lihue, Hawaii 96766. (808) 245-1507.

EMERGENCY MEDICINE

March 6-11—**9th Annual Mammoth Mt. Emergency Medicine Ski Conference.** UCI and Orange County Emergency Dept. Nurses Assoc. at Mammoth Lakes. Sun-Fri. 20 hrs. $350. Contact: CME Travel Services, 1615 S. Mission Road, Suite 3, Fallbrook 92028.

March 23-25—**Advances in Emergency Medicine.** UCSF at Holiday Inn Union Square, San Francisco. Wed-Fri. $300. Contact: UCSF.

March 25-26—**Advances in Emergency Medicine: Toxicology and Infectious Diseases.** UCLA at San Diego Hilton, Mission Bay. Fri-Sat. 9 hrs. Contact: UCLA.

May 11-15—**Tenth Annual Wound Management Workshop.** UCSD at San Diego Hilton Beach and Tennis Resort. Wed-Sun. 19 hrs. Contact: Edith S. Bookstein/WMW, PO Box 1386, La Jolla 92038. (619) 454-3212.

May 12-14—**Modern Concepts in Trauma Care Symposium.** Orange County Trauma Society at Disneyland Hotel, Anaheim. Thurs-Fri. 18 hrs. Contact: Orange County Trauma Society, (800) 368-0911.

June 6-10—**Topics in Emergency Medicine.** UCSF at Holiday Inn, Union Square, San Francisco. Mon-Fri. 32 hrs. $420. Contact: UCSF.

INTERNAL MEDICINE

February 19-21—**Update on Gastroenterology: Diagnosis and Therapy.** The Center for Health Education at the Newporter Resort, Newport Beach. Fri-Sun. Contact: The Center for Continuing Education, 2081 Atlantic Ave, PO Box 1428, Long Beach 90801-1428.

February 21-26—**Emergencies in Internal Medicine: 11th Annual UCD Winter Conference.** UCD at Hyatt Lake Tahoe, Incline Village, Nevada. Sun-Fri. 23 hrs. $395. Contact: UCD.

March 4-5—**Gastrointestinal Endoscopy 1988.** Southern California Society for Gastrointestinal Endoscopy at Century Plaza Hotel, Los Angeles. Fri-Sat. Contact: David S. Cantor, MD, 50 Alessandro, Ste 410, Pasadena 91105. (818) 793-7114.

March 9-10—**Advances in Endocrinology and Metabolism.** UCSF at Holiday Inn Union Square, San Francisco. Wed-Thurs. $250/$150. Contact: UCSF.

March 11-17—**Internal Medicine 1988: A Comprehensive Review.** Sharp Memorial Hospital at Hotel Del Coronado, Coronado. Fri-Thurs. 54 hrs. $495. Contact: Jackie Shiller, Continuing Medical Education Associates, PO Box 84296, San Diego 92138. (619) 223-2997.

March 16-19—**Frontiers in Clinical Rheumatology.** UCD at Clarion Inn, Napa. Wed-Sat. Contact: UCD.

March 17-18—**Diseases of the Urinary Tract.** Stanford University Medical Center at Hyatt Rickeys Hotel, Palo Alto. Thurs-Fri. 15 hrs. $300. Contact: Stanford.

March 18-20—**6th Carl M. Person Memorial Symposium: Frontiers of Rhematology.** Annenberg Center for Health Sciences at Palm Springs. Fri-Sun. 15.5 hrs. Contact: Annenberg Center, 39000 Bob Hope Dr, Rancho Mirage, 92270-3298. (800) 321-3690.

April 16-23—**Internal Medicine.** Stanford University Medical Center at The Westin Mauna Kea, Hawaii. Sun-Fri. 25 hrs. $495. Contact: Stanford.

May 23-27—**Advances in Internal Medicine.** UCSF at Sheraton-Palace Hotel, San Francisco. Mon-Fri. 32 hrs. $440. Contact: UCSF.

June 6-10—**Advances in Internal Medicine.** UCSF at Cole Hall. 32 hrs. $440. Contact: UCSF.

June 15-17—**Gastroenterology: Advances in Diagnosis and Management.** UCSF at The Mark Hopkins Hotel, San Francisco. Wed-Fri. 17 hrs. $375. Contact: UCSF.

OB/GYN

February 19-21—**Office Gynecology for the Primary Care Physician.** San Diego State University at Hyatt Islandia, San Diego. Fri-Sun. 18 hrs. $295. Contact: J. Shiller, Continuing Medical Education Associates, PO Box 84296, San Diego, 92138. (619) 223-2997.

March 16-19—**5th Annual Horizon in Reproductive Health Medical Conference.** UCSD at Hotel del Coronado, Coronado. Wed-Sat. Contact: Mary Fessel, 2100 5th Ave., San Diego, 92101. (619) 231-6760.

March 25-26—**GYN/Urology.** UCI at Hilton Riviera, Palm Springs. Fri-Sat. Contact: UCI.

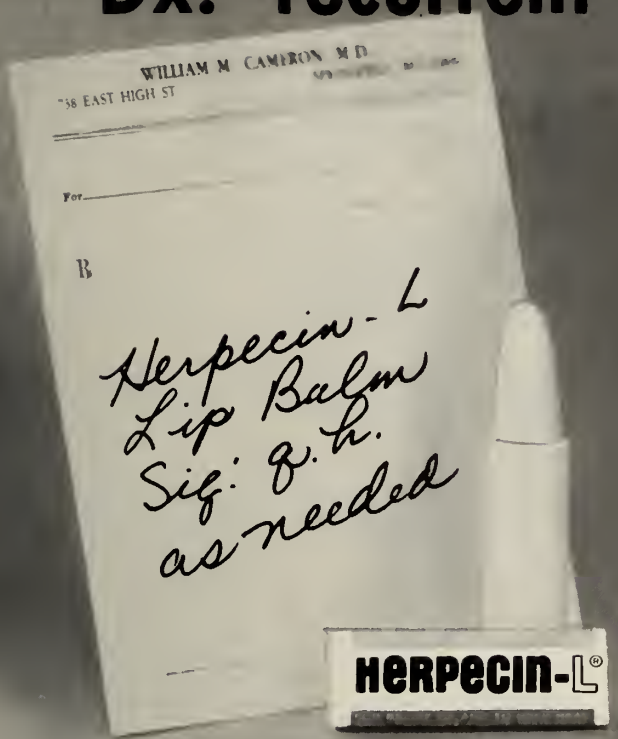
April 21-23—**10th Annual Orange County OB/GYN Congress.** Orange County Obstetrical and Gynecological Society at Westin Hotel, South Coast Plaza, Costa Mesa. Thur-Sat. 15 hrs. $300. Contact: Paula Rogers, PO Box 1297, Orange 92668. (714) 978-1260.

June 30-July 3—**6th Annual Controversies in Obstetrics & Gynecology.** Center for Health Education at Mauna Kea Beach Hotel, Hawaii. Thur-Sun. Contact: The Center for Health Education, 2081 Atlantic Ave., PO Box 1428, Long Beach, 90801-1428. (213) 595-3811.

August 19-21—**1988—Office Gynecology for the Primary Care Physician.** Continuing Medical Education Associates and San Diego State University at Hyatt Islandia, San Diego. Fri-Sun. 18 hrs. $295. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

(Continued on Page 241)

Dx: recurrent herpes labialis



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CONTINUING MEDICAL EDUCATION

(Continued from Page 240)

OPHTHALMOLOGY

March 18—**Visions in Ophthalmology '88.** Scripps Memorial Hospital at La Jolla Marriott, San Diego. Fri. 6 hrs. $75. Contact: Nomi Feldman, Conference Coordinator, 3770 Tansy St, San Diego 92121. (619) 453-6222.

PEDIATRICS

February 20-27—**Pediatric Emergencies.** Scripps Memorial Hospital, Encinitas and American Institute of Postgraduate Education at Royal Lahaina Resort, Maui. One week. 21 hrs. $395. Contact: Edith S. Bookstein/AIPE, PO Box 2586, La Jolla 92038. (619) 454-3212.

February 22-24—**Pediatrics Update 1988.** San Diego State University at Hyatt Islandia, San Diego. Mon-Wed. 18 hrs. $295. Contact: J. Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

March 12—**Behavioral/Development Pediatrics Symposium: Stress, Vulnerability and Child Health.** UCSF. Sat. 6.5 hrs. Contact: UCSF.

March 18-19—**Hematology: Neonatal, Pediatric & AIDS Related Issues.** Children's Hospital Oakland at Berkeley Marina Marriott Hotel, Fri-Sat. 11 hrs. Contact: Kim Leadon, CME Dept. Children's Hospital, 747 52nd Street, Oakland 94609. (415) 428-3021.

April 8-9—**UCD Annual Pediatrics Program.** UCD at Red Lion Motor Inn, Sacramento. Fri-Sat. Contact: UCD.

April 29-30—**21st Annual Advances and Controversies in Clinical Pediatrics.** UCSF at Mark Hopkins Hotel, San Francisco. Fri-Sat. 16.5 hrs. Contact: UCSF.

August 22-24—**Pediatrics Update: 1988.** San Diego State University at Hyatt Islandia, San Diego. Mon-Wed. 18 hrs. $295. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

October 22-29—**13th Annual Pediatrics for the Practitioner: A Pediatric Symposium.** Center for Health Education at Mauna Kea Beach Hotel, Hawaii. One week. Contact: The Center for Health Education, PO Box 1428, Long Beach 90801-1428.

PSYCHIATRY

March 27-31—**Adapting to Social Change, Therapy, Technology and Services.** American Orthopsychiatric Association at Hilton Square, San Francisco. Sun-Thurs. Contact: ORTHO, 19 W 44th St, #1616, New York, NY 10036. (212) 354-5770.

April 15-16—**3rd Annual Work and Mental Health Symposium.** UCSF at Holiday Inn Union Square, San Francisco. Fri-Sat. 12 hrs. $200. Contact: UCSF.

April 23-24—**The Cutting Edge 1988: Innovations in Psychotherapy: Helping Individuals and Couples to Change.** UCSD at Hotel Del Coronado, San Diego. Sat-Sun. 13 hrs. $275. Contact: UCSD.

May 23-24—**Child Abuse.** UCD at Holiday Inn Holidome, Sacramento. Mon-Tue. Contact: UCD.

RADIOLOGY

February 21-24—**7th Annual UCSD Imaging & Intervention Conference.** UCSD, Dept. of Radiology at Hotel Inter-Continental, San Diego. Sun-Wed. 25 hrs. $400. Contact: Mary J. Ryals, PO Box 920113, Norcross, GA 30092-0113. (404) 641-9773.

February 29-March 4—**Sierra Radiology Conference.** Sacramento Radiology Research and Education Foundation at Hyatt Lake Tahoe, Nevada. Mon-Fri. 20 hrs. $385. Contact: John McGahan, MD, Director, Sacramento Radiology and Research Foundation, PO Box 19184, Sacramento 95819. (916) 453-3766.

(Continued on Page 242)

CONTINUING MEDICAL EDUCATION

(Continued from Page 241)

March 7-11—**Neuroradiology Update.** UCSD at Hotel Del Coronado, San Diego, Mon-Fri. Up to 28 hrs. Contact: Mary J. Ryals, PO Box 920113, Norcross, GA 30092-0113. (404) 641-9773.

March 9-11—**8th Annual Current Approaches to Radiation, Oncology, Biology and Physics.** UCSF at Hotel Nikko, San Francisco. Wed-Fri. 18 hrs. Contact: The Crest Organization, Outside CA (800) 222-8882; Inside CA (415) 595-2704.

April 10-15—**8th Annual San Diego Resident's Radiology Review Course.** UCSD at Town & Country Hotel, San Diego. Sun-Fri. Contact: Mary J. Ryals, PO Box 920113, Norcross, GA 30092-0113. (404) 641-9773.

April 29-May 1—**13th Annual Spring Diagnostic Ultrasound Conference.** Los Angeles Radiological Society at Century Plaza Hotel, Los Angeles. Fri-Sun. 20 hrs. $325. Contact: Christopher M. Rose, MD, c/o Los Angeles Radiological Society—SDUC, PO Box 91215, Los Angeles 90009-1215. (213) 642-0921.

May 3-7—**8th Annual Post Conference Seminar.** Los Angeles Radiology Society at Kahala Hilton Hotel, Honolulu. Tues-Sat. 19 hrs. $395. Contact: Christopher Rose, MD, c/o Los Angeles Radiological Society—SDUC, PO Box 91215, Los Angeles 90009-1215. (213) 642-0921.

SPORTS MEDICINE

January 17-22—**Sports Medicine: 1988.** UCD at Hyatt Lake Tahoe, Nevada. Sun-Fri. 28 hrs. $435. Contact: UCD.

SURGERY

February 20-21—**Advances in Sclerotherapy and Advances in Surgical and Medical Treatment of Venous Diseases.** Scripps Clinic and Research Foundation at Sheraton Grand Hotel, San Diego. Sat-Sun. 9 hrs. $125. Contact: Helane Fronek, MD, 3051 Cranbrook Ct, La Jolla 92037

March 3-6—**Surgical Forum.** Society of Graduate Surgeons of the Los Angeles County/University of Southern California Medical Center at the Biltmore Hotel, Los Angeles. Thurs-Sun. 25 hrs. $400. Contact: Society of Graduate Surgeons, 5820 Wilshire Blvd, Suite 500, Los Angeles 90036.

March 14-17—**Controversies in General and Vascular Surgery.** UCLA at Palm Springs Spa Hotel, Palm Springs. Mon-Thurs. Contact: UCLA.

March 17-20—**The International Symposium on Hair Replacement Surgery.** American Academy of Facial Plastic and Reconstructive Surgery at Four Seasons Hotel, Los Angeles. Thurs-Sun. 30 hrs. Contact: AAFPRS Foundation, 1101 Vermont Ave, NW, Suite 404, Washington, DC, 20005.

April 14-16—**Postgraduate Course in General Surgery.** UCSF. Thur-Sat. Contact: UCSF.

April 15-17—**The 5th Annual San Diego Meeting on Arthroscopic Surgery of the Shoulder.** Tri-City Orthopaedic & Sports Physical Therapy Medical Group, Inc. at La Jolla Marriott Hotel, La Jolla. Fri-Sun. Contact: James C. Esch, MD, 3905 Waring Rd, Oceanside 92056. (619) 724-9000.

April 16-23—**Management of the Surgical Patient.** Stanford University Medical Center at The Westin Mauna Kea, Hawaii. Sun-Fri. 25 hrs. $495. Contact: Stanford.

OF INTEREST TO ALL PHYSICIANS

February 18-19—**Video Display Terminal Safety.** USC. Thur-Fri. $265. Contact: USC.

February 19-21—**Diagnosis and Management of Respiratory Disease.** Medical Education Resources at Wyndham Hotel, Palm Springs. Fri-Sat. 11-13 hrs. $225-$295. Contact: MER, 5808 S. Rapp St., Suite 202, Littleton, CO 80120. (800) 421-3756.

February 19-21—**New Precepts and Concepts in Dermatopathology.** Desert Hospital, Palm Springs at Desert Hospital. Fri-Sun. 14 hrs. $350. Contact: Charles Steffen, MD, 1111 Tahquitz East, Ste 102A, Palm Springs 92262.

February 29-March 4—**Basic Science for Clinicians.** Stanford University Medical Center at Tresidder Memorial Union, Stanford. Mon-Fri. 25.75 hrs. $495. Contact: Stanford.

March 2-5—**Annual Review in Family Medicine: Controversies and Challenges in Primary Care.** UCSF at Stanford Court Hotel, San Francisco. Wed-Sat. 17 hrs. Contact: UCSF.

March 4—**6th Annual Geriatrics Symposium.** Sutter Health at Red Lion Inn, Sacramento. Fri. 7 hrs. Contact: Sutter Health, CME Dept. 2020 I St, Suite D, Sacramento 95814. (916) 446-7681.

March 4—**14th Annual Diabetes Program.** UCD at Capitol Plaza Holiday Inn, Sacramento. Contact: UCD.

March 4-9—**Western Scientific Assembly.** CMA at Bally's Hotel, Reno, Nevada. Thur-Sun. Contact: Susan Schaefer, CMA, PO Box 7690, San Francisco, 94120-7690. (415) 863-5522 Ext. 404.

March 4-10—**56th Annual Postgraduate Convention.** LLU. Fri-Thur. 35 hrs. Contact: LLU.

March 9—**Environmental and Occupational Medicine Symposium.** Enloe Memorial Hospital and Chico Community Hospital at The Esplanade Building, Enloe Hospital, Chico. Wed. 6 hrs. Contact: Bonnie Wells, 5th Ave and the Esplanade, Chico 95926. (916) 891-7375.

March 11-12—**Sleep Disorders Medicine: Medical Management.** Scripps Clinic and Research Foundation. Fri-Sat. 12 hrs. $200. Contact: Bonny Mower, 10666 N. Torrey Pines Road, La Jolla, 92037. (619) 457-8556.

March 11-12—**Diabetes Update.** UCSF at Holiday Inn Union Square, San Francisco. Fri-Sat. Contact: UCSF.

March 12-13—**4th Annual Sierra Arthritis Symposium: State of the Art Diagnosis and Treatment of Arthritis.** Community Hospital of Fresno and California Sierra Arthritic Foundation at Ahwahnee Hotel, Yosemite. Sat-Sun. 7 hrs. $95. Contact: Gloria Fitzgerald, Education and Training Department, PO Box 1232, Fresno 93715. (209) 442-3932.

March 14-17—**Critical Care Medicine: 26th Annual Symposium.** USC at Caesars Palace Hotel, Las Vegas. Mon-Thurs. Contact: USC.

March 16-19—**5th Annual Horizon in Reproductive Health Medical Conference.** UCSD at Hotel Del Coronado, Coronado. Wed-Sat. Contact: Mary Fessel, 2100 5th Ave., San Diego, 90101. (619) 231-6760.

March 18-19—**Hematology: Neonatal, Pediatric and AIDS Related Issues.** Children's Hospital, Oakland at Berkeley Marina Marriott Hotel. Fri-Sat. 11 hrs. Contact: Kim Leadon, CME Department, Children's Hospital, 747 52nd St, Oakland 94609. (415) 428-3021.

March 19—**3rd Annual Symposium on Women's Health.** Sutter Health at Board of Realtors Building, Sacramento. Sat. 6 hrs. $45. Contact: Sutter Health, CME Department, 2020 I St, Suite D, Sacramento 95414. (916) 446-7681.

March 19—**Inpatient Vs. Outpatient Treatment: How to Decide.** California Society for the Treatment of Alcoholism & Other Drug Dependencies at Ramada Renaissance Hotel, San Francisco. Sat. Contact: Corinne Parker, 3803 Broadway, Suite 2, Oakland, 94611. (415) 428-9091.

March 19-21—**Transfusion—Associated Infections and Immune Response.** UCSF at Fairmont Hotel, San Francisco. Sat-Mon. Contact: UCSF.

March 25—**Infectious Diseases for Pulmonary and Critical Care Specialists.** UCSF and Samuel Merritt Hospital at San Francisco. Fri. 7 hrs. $170. Contact: UCSF.

March 25-26—**Toxicology and Infectious Disease.** UCLA at San Diego Hilton Beach & Tennis Resort. Fri-Sat. 9 hrs. $146.25. Contact: UCLA.

March 26—**7th Annual Nora Eccles Harrison Symposium.** UCLA at Los Angeles. Sat. 7 hrs. $45. Contact: UCLA.

March 26-April 2—**Orthopedic Emergencies.** Scripps Memorial Hospital, Encinitas and American Institute of Postgraduate Education at Waiohai and Poipu Beach Hotels, Kauai. One week. 21 hrs. $395. Contact: Edith S. Bookstein/AIPE, PO Box 2586, La Jolla 92038. (619) 454-3212.

March 26-April 2—**Behavioral Medicine for the Family Physician.** University of Arizona at Kona, Hawaii. One week. 24 hrs. Contact: Kathy Rairigh, Epic Expeditions, P.O. Box 209, Sun Valley, Idaho 83353. (208) 788-4995.

April 10-15—**Advanced Methods in Pharmacokinetics and Pharmacodynamics.** UCSF. Sun-Fri. Contact: UCSF.

April 13-15—**9th Annual Advances in Infectious Diseases: Current Therapy.** UCSF at Sheraton-Palace Hotel, San Francisco. Wed-Fri. 16 hrs. $365. Contact: UCSF.

(Continued on Page 243)

CONTINUING MEDICAL EDUCATION

(Continued from Page 242)

April 13-17—**Annual Scientific Program and Postgraduate Courses.** Pacific Coast Fertility Society at Desert Princess Resort, Palm Springs. Wed-Sun. 22 hrs. Contact: Pacific Coast Fertility Society, 5820 Wilshire Blvd, #500, Los Angeles 90036. (213) 937-5514.

April 15-17—**Office Orthopedics for the Primary Care Physicians.** CMEA & Sharp Memorial Hospital at San Diego Princess Hotel. Fri-Sun. 20 hrs. $395. Contact: Jacqueline Shiller, P.O. Box 84296, San Diego, 92138. (619) 223-2997.

April 16-23—**Current Concepts in Allergy and Clinical Immunology.** University of Washington at Maui, Hawaii. One week. Contact: U/W School of Medicine, Div of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

April 22-23—**Comprehensive Care of the AIDS Patient: A Workshop.** UCSF at San Francisco. Fri-Sat. Contact: UCSF.

April 23—**Current Concepts in Liver Diseases.** Scripps Clinic and Research Foundation at Amphitheater, Scripps Clinic, La Jolla. Thur. 6 hrs. $125. Contact: Bonny Mower, 10666 N. Torrey Pines Road, La Jolla, 92037. (619) 457-8556.

May 6-8—**Diagnosis and Management of Respiratory Diseases.** Medical Education Resources at Ceasars Palace, Las Vegas, Nevada. Fri-Sun. 11-13 hrs. $225-$295. Contact: MER, 5080 S. Rapp St., Suite 202, Littleton, CO 80120. (800) 421-3756.

May 15-20—**Primary Care Medicine: Update '88.** UCSF at the Waiohai Hotel, Hawaii. Sun-Fri. 20 hrs. $425. Contact: UCSF.

May 26-27—**Current Concepts of Anatomic Pathology.** UCSF. Thur-Fri. Contact: UCSF.

June 13-17—**Family Practice Refresher Course.** UCI at Sheraton Newport, Newport Beach. Mon-Fri. 44.5 hrs. $575. Contact: UCI.

June 13-18—**UCI Family Practice Refresher Course.** UCI and Memorial Medical Center at Sheraton Newport Hotel, Newport Beach. Mon-Sat. Contact: Memorial Medical Center, PO Box 1428, Long Beach 90801-1428. (213) 595-3811.

June 18-19—**Skills Workshop: Flexible Sigmoidoscopy and Colposcopy.** UCI at Sheraton Newport, Newport Beach. Sat-Sun. 16 hrs. $140-ea., $250-both. Contact: UCI.

June 25-26—**10th Annual Poison Control Center Symposium on Toxicology and Poisoning.** UCSF and Continuing Medical Education in Pharmacy at San Francisco. Sat-Sun. 14 hrs. $235. Contact: Continuing Education S/P, UCSF, Box 0446, San Francisco 94143. (415) 476-4194.

July 15-18—**Caring for People with AIDS and Their Loved Ones.** Concern for Dying: an Educational Council, at Bishop's Ranch, Healdsburg. Fri-Mon. Contact: Penny Weingarten, 250 West 57th St., Room 831, New York, NY 10107. (800) 248-2122.

August 3-6—**15th Annual Meeting: The Peruvian American Medical Society** at Westin Bonaventure Hotel, Los Angeles. Wed-Sat. Contact: Hugo Ortiz, MD, Chairman, Scientific Program, 6488 Tamerlane Dr, West Bloomfield, MI 48322.

IDAHO

February 13-20—**Controversies in Pulmonary Medicine.** University of Arizona College of Medicine, Department of Family and Community Medicine, and Epic Expeditions at Sun Valley. One week. 24 hrs. Contact: Kathy Rairigh, PO Box 209, Sun Valley 83353. (208) 788-4995.

February 20-27—**Drug Therapy in Maternal-Fetal Medicine.** University of Washington School of Medicine at Sun Valley. One week. Contact: U/W School of Medicine, Div of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

February 20-27—**Effective Treatment of Common Sports Injuries.** University of Arizona College of Medicine, Department of Family and Community Medicine, and Epic Expeditions at Sun Valley. One week. 24 hrs. Contact: Kathy Rairigh, PO Box 209, Sun Valley 83353. (208) 788-4995.

March 4-6—**29th Annual Medical Winter Clinics—"You and Your Health."** Ada County Medical Society at Shore Lodge—Brundage Mountain for Alpine Powder and Nordic Skiing, McCall, Idaho. Fri-Sun. 11 hrs. $125. Contact: Judy Barningham, Ada County Medical Society, PO Box 2668, Boise 83701. (208) 336-2930.

(Continued on Page 244)

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INDICATIONS AND USAGE: BECAUSE OF REPORTS OF INTESTINAL AND GASTRIC ULCERATION AND BLEEDING WITH SLOW-RELEASE POTASSIUM CHLORIDE PREPARATIONS, THESE DRUGS SHOULD BE RESERVED FOR THOSE PATIENTS WHO CANNOT TOLERATE OR REFUSE TO TAKE LIQUID OR EFFERVESCENT POTASSIUM PREPARATIONS OR FOR PATIENTS IN WHOM THERE IS A PROBLEM OF COMPLIANCE WITH THESE PREPARATIONS.

1. For therapeutic use in patients with hypokalemia with or without metabolic alkalosis, in digitalis intoxication and in patients with hypokalemic familial periodic paralysis.
2. For the prevention of potassium depletion when the dietary intake is inadequate in the following conditions: Patients receiving digitalis and diuretics for congestive heart failure, hepatic cirrhosis with ascites, states of aldosterone excess with normal renal function, potassium-losing nephropathy, and with certain diarrheal states.
3. The use of potassium salts in patients receiving diuretics for uncomplicated essential hypertension is often unnecessary when such patients have a normal dietary pattern. Serum potassium should be checked periodically, however, and if hypokalemia occurs, dietary supplementation with potassium-containing foods may be adequate to control milder cases. In more severe cases supplementation with potassium salts may be indicated

CONTRAINDICATIONS: Potassium supplements are contraindicated in patients with hyperkalemia since a further increase in serum potassium concentration in such patients can produce cardiac arrest. Hyperkalemia may complicate any of the following conditions: Chronic renal failure, systemic acidosis such as diabetic acidosis, acute dehydration, extensive tissue breakdown as in severe burns, adrenal insufficiency, or the administration of a potassium-sparing diuretic (e.g., spironolactone, triamterene).

Wax-matrix potassium chloride preparations have produced esophageal ulceration in certain cardiac patients with esophageal compression due to enlarged left atrium.

All solid dosage forms of potassium chloride supplements are contraindicated in any patient in whom there is cause for arrest or delay in tablet passage through the gastrointestinal tract. In these instances, potassium supplementation should be with a liquid preparation.

WARNINGS: Hyperkalemia—In patients with impaired mechanisms for excreting potassium, the administration of potassium salts can produce hyperkalemia and cardiac arrest. This occurs most commonly in patients given potassium by the intravenous route but may also occur in patients given potassium orally. Potentially fatal hyperkalemia can develop rapidly and be asymptomatic. The use of potassium salts in patients with chronic renal disease, or any other condition which impairs potassium excretion, requires particularly careful monitoring of the serum potassium concentration and appropriate dosage adjustment.

Interaction with Potassium Sparing Diuretics—Hypokalemia should not be treated by the concomitant administration of potassium salts and a potassium-sparing diuretic (e.g., spironolactone or triamterene) since the simultaneous administration of these agents can produce severe hyperkalemia.

Gastrointestinal Lesions—Potassium chloride tablets have produced stenotic and/or ulcerative lesions of the small bowel and deaths. These lesions are caused by a high localized concentration of potassium ion in the region of a rapidly dissolving tablet, which injures the bowel wall and thereby produces obstruction, hemorrhage or perforation.

K-DUR tablets contain micro-crystalloids which disperse upon disintegration of the tablet. These micro-crystalloids are formulated to provide a controlled release of potassium chloride. The dispersibility of the micro-crystalloids and the controlled release of ions from them are intended to minimize the possibility of a high local concentration near the gastrointestinal mucosa and the ability of the KCl to cause stenosis or ulceration. Other means of accomplishing this (e.g., incorporation of potassium chloride into a wax matrix) have reduced the frequency of such lesions to less than one per 100,000 patient years (compared to 40–50 per 100,000 patient years with enteric-coated potassium chloride) but have not eliminated them. The frequency of GI lesions with K-DUR tablets is, at present, unknown. K-DUR tablets should be discontinued immediately and the possibility of bowel obstruction or perforation considered if severe vomiting, abdominal pain, distention, or gastrointestinal bleeding occurs.

Metabolic Acidosis—Hypokalemia in patients with metabolic acidosis should be treated with an alkalinizing potassium salt such as potassium bicarbonate, potassium citrate, potassium acetate, or potassium gluconate.

PRECAUTIONS: The diagnosis of potassium depletion is ordinarily made by demonstrating hypokalemia in a patient with a clinical history suggesting some cause for potassium depletion. In interpreting the serum potassium level, the physician should bear in mind that acute alkalosis per se can produce hypokalemia in the absence of a deficit in total body potassium while acute acidosis per se can increase the serum potassium concentration into the normal range even in the presence of a reduced total body potassium. The treatment of potassium depletion, particularly in the presence of cardiac disease, renal disease, or acidosis requires careful attention to acid-base balance and appropriate monitoring of serum electrolytes, the electrocardiogram, and the clinical status of the patient.

Laboratory Tests: Regular serum potassium determinations are recommended. In addition, during the treatment of potassium depletion, careful attention should be paid to acid-base balance, other serum electrolyte levels, the electrocardiogram, and the clinical status of the patient, particularly in the presence of cardiac disease, renal disease, or acidosis.

Drug Interactions: Potassium-sparing diuretics; see **WARNINGS**.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term carcinogenicity studies in animals have not been performed.

Pregnancy Category C: Animal reproduction studies have not been conducted with K-DUR. It is also not known whether K-DUR can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. K-DUR should be given to a pregnant woman only if clearly needed.

Nursing Mothers: The normal potassium ion content of human milk is about 13 mEq per liter. Since oral potassium becomes part of the body potassium pool, so long as body potassium is not excessive, the contribution of potassium chloride supplementation should have little or no effect on the level in human milk.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: One of the most severe adverse effects is hyperkalemia (see **CONTRAINDICATIONS, WARNINGS,** and **OVERDOSAGE**). There have also been reports of upper and lower gastrointestinal conditions including obstruction, bleeding, ulceration, and perforation (see **CONTRAINDICATIONS** and **WARNINGS**); other factors known to be associated with such conditions were present in many of these patients.

The most common adverse reactions to oral potassium salts are nausea, vomiting, abdominal discomfort, and diarrhea. These symptoms are due to irritation of the gastrointestinal tract and are best managed by taking the dose with meals or reducing the dose.

Skin rash has been reported rarely.

OVERDOSAGE: The administration of oral potassium salts to persons with normal excretory mechanisms for potassium rarely causes serious hyperkalemia. However, if excretory mechanisms are impaired or if potassium is administered too rapidly intravenously, potentially fatal hyperkalemia can result (see **CONTRAINDICATIONS** and **WARNINGS**). It is important to recognize that hyperkalemia is usually asymptomatic and may be manifested only by an increased serum potassium concentration and characteristic electrocardiographic changes (peaking of T-waves, loss of P-waves, depression of S-T segment, and prolongation of the QT-interval). Late manifestations include muscle-paralysis and cardiovascular collapse from cardiac arrest.

Treatment measures for hyperkalemia include the following:

1. Elimination of foods and medications containing potassium and of potassium-sparing diuretics.
2. Intravenous administration of 300 to 500 ml/hr of 10% dextrose solution containing 10–20 units of insulin per 1,000 ml.
3. Correction of acidosis, if present, with intravenous sodium bicarbonate.
4. Use of exchange resins, hemodialysis, or peritoneal dialysis.

In treating hyperkalemia, it should be recalled that in patients who have been stabilized on digitalis, too rapid a lowering of the serum potassium concentration can produce digitalis toxicity

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CONTINUING MEDICAL EDUCATION

(Continued from Page 243)

March 12-19—**Strategies for Fitness and Health Promotion.** University of Arizona College of Medicine, Department of Family and Community Medicine, and Epic Expeditions at Sun Valley. One week. 24 hrs. Contact: Kathy Rairigh, PO Box 209, Sun Valley 83353. (208) 788-4995.

March 17-18—**Idaho Thoracic Society—Annual Medical Symposium.** Anderson Center, Boise. Contact: Idaho Thoracic Society, 2621 Camas St, Boise 83705. (208) 344-6567.

MONTANA

February 18-20—**7th Annual Big Sky Pulmonary Ski Conference.** American Lung Association of Montana at Big Sky of Montana. Thurs-Sat. Contact: ALA of Montana, 825 Helena Ave, Helena 59601. (406) 442-6556 or 1 (800) 252-6368 (in Montana).

NEW MEXICO

Information, requests for accreditation and items to be listed should be sent to the chairman of the CME Committee, New Mexico Medical Society, 303 San Mateo NE, Suite 204, Albuquerque, NM 87108 at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 266-7868.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

February 25-27—**21st Annual OB/GYN Postgraduate Seminar.** Holiday Inn Pyramid Plaza, Albuquerque. Contact: UNM SOM, Office of CME, (505) 277-3942.

February 25-27—**Santa Fe Ski Symposium—Hypertension—1988.** Santa Fe. Thurs-Sat. Contact: National Kidney Foundation of New Mexico, 1715 Girard, NE, Albuquerque 87106. (505) 266-4573.

February 26-28—**16th Annual Thoracic Society Lung Disease Symposium.** Santa Fe Hilton. Fri-Sun. Contact: Lung Association, (505) 265-0732.

March 2-5—**Taos Metabolism Seminar.** Quail Ridge Inn, Taos. Contact: Martin J. Conway, MD, Lovelace Medical Center, 5400 Gibson SE, Albuquerque 87108. (505) 262-7000.

March 4-5—**Advances in Internal Medicine '88.** Veterans Administration Medical Center, Albuquerque. Contact: UNM SOM, Office of CME, (505) 277-3942.

March 11—**The Physician in Crisis.** Presbyterian Hospital Quality of Life Committee. Contact: Office of Medical Education, (505) 841-1225.

March 12—**NM Pediatric Society Wylder Lecture—Mother to Child Infection.** UNM School of Pharmacy Auditorium. Contact: Marilyn Stark, NM Pediatric Society, (505) 265-7431.

April 21-23—**10th Annual Pediatric Cardio-Pulmonary Update.** Sheraton Old Town, Albuquerque. Contact: UNM SOM, Office of CME, (505) 277-3942.

April 29-May 1—**Southwest Allergy Forum.** Eldorado Hotel, Sante Fe. Contact: UNM SOM, Office of CME, (505) 277-3942.

May 5-7—**NM Medical Society Annual Meeting—AIDS—Protecting the Health Professional and Chemical Dependency, Monitored Treatment Program. Loss Control Seminar,** Physicians Mutual Liability Insurance Co. Albuquerque Hilton Inn. Contact: NM Medical Society, (505) 266-7868.

May 14—**Cardiac Physical Diagnosis Symposium.** Contact: UNM SOM, Office of CME, (505) 277-3942.

(Continued on Page 246)

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(Continued from Page 244)

May 19-20—**Mental Health Services With Hispanic and Native American Children and Families.** Contact: UNM SOM, Office of CME, (505) 277-3942.

June 2-3—**8th Annual UNM/ACEP Emergency Medicine Symposium.** AMFAC Hotel, Albuquerque. Contact: UNM SOM, Office of CME, (505) 277-3942.

July 22-24—**Diagnosis and Management of Arrhythmia.** Contact: Presbyterian Heart Institute, Albuquerque, (505) 841-1065/(505) 242-2796.

UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the CME office of the Utah Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. They also must meet the definition of Utah Approved CME Credit for the purpose of medical license reregistration in Utah. Accredited institutions wishing to list AMA Category 1/Utah Approved CME courses here should send information at least two months in advance to the Office of Continuing Medical Education, 540 East Fifth South, Salt Lake City, Utah 84102; or phone (801) 355-5290. For information on CME accreditation or on the CME requirements of the Utah Physicians' Licensing Board, please write the CME office at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution or the CME office for current details.

SPONSORS OF COURSES—ABBREVIATIONS

AHA: American Heart Association, Utah Affiliate, 645 E 400 South, Salt Lake City 84102, (801) 322-5601.

BYUHS: Brigham Young University Health Services, McDonald Student Health Center, Brigham Young University, Provo 84602, (801) 378-2771.

CH: Castleview Hospital (formerly Carbon Hospital), RFD 2, Box 46, Price 84501, (801) 637-4800.

CWH: Cottonwood Hospital, 5770 S 300 East, Salt Lake City 84101, (801) 262-3461.

DMC: Dixie Medical Center, 544 S 400 East, St George 84770, (801) 673-9681.

HCH: Holy Cross Hospital, 1045 E First South, Salt Lake City 84102, (801) 350-4744

ITS: Intermountain Thoracic Society, 1616 S 11th East, Salt Lake City 84105, (801) 484-4456.

LDSH: LDS Hospital, 8th Ave and "C" St, Salt Lake City 84143, (801) 321-1100.

LRH: Logan Regional Hospital, 1400 N 5th East, Logan 84321, (801) 752-2050

MDH: McKay-Dee Hospital Center, 3939 Harrison Blvd, Ogden 84409 (801) 399-4141.

MVH: Mountain View Hospital, 1000 E Highway 6, Payson 84651, (801) 465-9201.

144: 144th Evacuation Hospital, PO Box 8000, Salt Lake City 84108, (801) 524-3924.

OSS: Ogden Surgical Society, PO Box 9311, Ogden 84409.

PCMC: Primary Children's Medical Center, 320 12th Ave, Salt Lake City 84103, (801) 363-1221.

PVH: Pioneer Valley Hospital, 3460 S 4155 West, West Valley City 84120, (801) 968-9061.

SMH: St Mark's Hospital, 1200 E 3900 South, Salt Lake City 84117, (801) 268-7111.

UOS: Utah Ophthalmological Society, 540 E 500 South, Salt Lake City 84102, (801) 355-7477.

USH: Utah State Hospital, PO Box 270, Provo 84603-0270, (801) 373-4400.

UUMC: University of Utah Medical Center, 50 N Medical Dr, Salt Lake City 84132, (801) 581-2258.

UVRMC: Utah Valley Regional Medical Center, 1034 N Fifth West, Provo 84604 (801) 373-7850.

VAMC: Veterans Administration Medical Center, 500 Foothill Dr, Salt Lake City 84148, (801) 582-1565.

VVMC: Valley View Medical Center, 595 S 75 East, Cedar City 84720, (801) 586-6587.

MEDICAL GRAND ROUNDS

Each Wed—8:00-9:00 a.m. Alternating between University of Utah Medical Center and VA Medical Center, Salt Lake City. Contact: William D. Odell, MD, PhD, Professor and Chairman, Dept of Internal Medicine, Univ of Utah, (801) 581-7606.

* * *

February 15-19—**11th Annual Update in Clinical Microbiology and Immunology** (Sponsor: UUMC). Mon-Fri. Park City Resort. Contact: M. Beckman, (801) 581-7480.

February 17-20—**29th Annual OB-GYN Update** (Sponsor: UUMC). Wed-Sat. Snowbird Resort. Contact: Sheryl Martin, (801) 581-5501.

February 19-23—**33rd Annual Postgrad Course in Anesthesiology** (Sponsor: UUMC). Fri-Tues. Salt Lake City. Contact: Vicky Larsen, (801) 581-6393.

February 21-28—**Intermountain Dermatology Meeting** (Sponsor: UUMC). Sun-Sun. Colorado. Contact: Bernie Lasalle, (801) 581-7837.

February 24-27—**Reproductive Endocrinology and Infertility** (Sponsor: UUMC). Wed-Sat. Snowbird Resort. Contact: Sheryl Martin, (801) 581-5501.

February 24-27—**Pediatric Emergency Medicine** (Sponsor: UUMC). Wed-Sat. Salt Lake City. Contact: Amy Eschelman, (801) 521-1221.

February 28-March 4—**Vascular Imaging: Update on Interventional Radiology** (Sponsor: UUMC). Sun-Fri. Snowbird Resort. Contact: (801) 581-8188.

February 29-March 4—**Advances in Internal Medicine** (Sponsor: UUMC). Mon-Fri. Snowbird Resort. Contact: Jennifer Fossum, (801) 581-3581.

March 7-11—**Gastroenterology Update** (Sponsor: UUMC). Mon-Fri. Snowbird Resort. Contact: Jennifer Fossum, (801) 581-3581.

March 1988—**Nutrition in Contemporary Medicine** (Sponsor: UUMC). Contact: Jennifer Fossum, (801) 581-3581.

March 30-April 1—**Common Problems in Pediatrics** (Sponsor: UUMC). Wed-Fri. Contact: K. Blosch, (801) 466-3500.

WASHINGTON

This listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. To list Category 1 programs here please send information at least two months in advance to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 900, Seattle, WA 98121; or phone (206) 441-WSMA.

Brochures and registration forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

February 19-20—**Medicine for Psychotherapists.** Seattle. Fri-Sat. Contact: VMMC.

February 25-26—**Survivorship.** Spokane. Thurs-Fri. Contact: Carolyn Hunter, (509) 325-6146.

COURSE SPONSORS AND CONTACT INFORMATION

CME HARBORVIEW—Contact: Gayle Splater, Cytology Continuing Education, Dept. of Pathology, Harborview Medical Center, 325 Ninth Avenue, Seattle, WA 98104, (206) 223-5953.

CME PIERCE COUNTY—Contact: Mrs Maxine Bailey, Executive Director, College of Medical Education, 705 South Ninth, No. 203, Tacoma, WA 98405, (206) 627-7137.

U/W (UNIVERSITY OF WASHINGTON)—Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195, (206) 543-1050.

WSMA—Washington State Medical Association, Continuing Medical Education, 2033 Sixth Ave, Suite 900, Seattle, WA 98121, (206) 441-9762.

VMMC (VIRGINIA MASON MEDICAL CENTER)—Contact: Linda Orgel, Division of Continuing Medical Education, Virginia Mason Medical Center, PO Box 900, Seattle, WA 98111, (206) 223-6898.

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*▲ Richard S. Weiner, Ph.D., Director
Fellow and Diplomate in Medical Psychotherapy Board Certified in Behavioral Medicine, Certified Family Mediator, Board Certified Counselor, Fellow and Diplomate in Professional Counseling

* Joseph Lee, M.D. ▶
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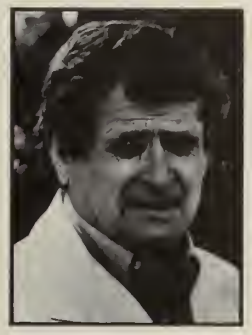

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Pawan Chadha, M.D. ▶
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*Member: International Association for the Study of Pain, American Association for the Study of Pain, Western USA Pain Society

*▲ Ward B. Studt, M.D., M.S.HA
Fellow American Academy of Orthopedic Surgeons, Fellow American College of Surgeons, Certified American Board of Orthopedic Surgeons

CONTINUING MEDICAL EDUCATION

(Continued from Page 246)

March 3-4—**Northwest Regional Rural Health Conference. Rural Health: Strategies and Solutions.** Spokane. Thurs-Fri. Contact: William Lassey, (509) 747-1012.

March 4-5—**Spokane Society of Internal Medicine—Annual CME Meeting: Weekend Athlete—Impact on Medical Practice in the 80s.** Spokane. Wed-Thurs. Contact: Curtis Wickre, MD, (509) 838-2531.

March 4-5—**Primary Care of Orthopaedics.** Seattle. Fri-Sat. Contact: Maria Lilja, (206) 543-1050.

March 4-5—**Soft Tissue Surgery.** Seattle. Fri-Sat. Contact: VMMC.

March 11—**Recent Developments in Occupational Medicine.** Fri. Contact: U/W, (206) 543-1069.

March 15—**Washington State Academy of Ophthalmology Monthly Meeting.** TBA. Tues. Contact: Patti Smith, (206) 441-9762.

March 18-19—**NW Regional Rural Health Conference. Rural Health: Strategies and Solutions.** Spokane. Fri-Sat. Contact: ICNE, (509) 325-6146.

March 19-23—**11th Annual Physical Medicine and Rehabilitation Review.** Seattle. Sat-Wed. Contact: Maria Lilja, (206) 543-1050.

March 19-23—**Death Investigation.** Seattle. Sat-Wed. Contact: Maria Lilja, (206) 543-1050.

March 19-26—**Advances in Drug Therapy.** Seattle. One week. Contact: U/W, (206) 543-1050.

March 23-25—**Spirometry Training for Worker Screening.** Seattle. Wed-Fri. Contact: U/W, (206) 543-1069.

March 24-25—**Current Issues in Nutrition.** Seattle. Thurs-Fri. Contact: U/W, (206) 543-1050.

March 25—**Update in Contrast Media: An Evening of Uroradiology.** Seattle. Fri. Contact: VMMC.

April 16-20—**American Radium Society—Seventieth Annual Meeting.** Seattle. Sat-Wed. Contact: Ms Suzanne Bohn, ARS, Philadelphia, PA. (215) 574-3179.

April 19—**Washington State Academy of Ophthalmology Monthly Meeting.** TBA. Tues. Contact: Pattie Smith, (206) 441-9762.

May 5-6—**Health Effects of Synthetic Fibers.** Seattle. Thurs-Fri. Contact: U/W, (206) 543-1069.

May 13—**Current Drug Topics—Pharmacology for the Practitioner.** Seattle. Fri. Contact: VMMC.

May 19-20—**Travel and Medicine.** Seattle. Thurs-Fri. Contact: Maria Lilja, (206) 543-1050.

May 19-21—**Emergency Medicine Update.** Seattle. Thurs-Sat. Contact: VMMC.

June 3—**Topics in General Internal Medicine.** Seattle. Fri. Contact: VMMC.

June 9-11—**Obstetric Ultrasound.** Seattle. Thurs-Sat. Contact: Robin Murray, (202) 863-2543.

June 20-24—**Pathology of Lung Cancer.** Seattle. Mon-Fri. Contact: VMMC.

July 29-31—**Seafair Anesthesia X.** Seattle. Fri-Sun. Contact: VMMC.

August 5—**Otology Update.** Seattle. Fri. Contact: VMMC.

WYOMING

February 28-March 6—**Strategies for Fitness and Health Promotion.** University of Arizona College of Medicine, Department of Family and Community Medicine, and Epic Expeditions at Jackson Hole. One week. 24 hrs. Contact: Kathy Rairigh, PO Box 209, Sun Valley, ID 83353. (208) 788-4995. ◆

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INTERNAL MEDICINE—CENTRAL UTAH. Seeking General Internist and/or Internist with subspecialty in Endocrinology or Infectious Disease to join established Internal Medicine clinic. 350-bed hospital across the street. First year salary with possible partnership after first year. Inquire: Dorothy Farnworth, Central Utah Medical Clinic, 1055 North 500 West, Provo, UT 84601.

WE HAVE FULL- AND PART-TIME LOCUM TENENS opportunities available with guaranteed incomes and paid malpractice. For more information, contact John Smith, Locum Tenens, Inc (A Division of Jackson and Coker), 400 Perimeter Center Terrace, Ste 760 WJM, Atlanta, GA 30346; Tel. 1 (800) 544-1987.

ARIZONA-BASED PHYSICIAN recruiting firm has opportunities coast-to-coast. "Quality Physicians for Quality Clients since 1972." Call (602) 990-8080; or send CV to Mitchell & Associates, Inc, PO Box 1804, Scottsdale, AZ 85252.

SOUTH CENTRAL WYOMING. Immediate practice opportunity for BC/BE Urologist. Well-equipped JCAH hospital for a service area of approximately 20,000 population. No state or city income tax. Relocation incentives. Superior hunting, fishing, camping, snowmobiling. Three hours to Colorado ski area, five hours to Jackson Hole. One and one-half hours to the mountains. If interested, please send CV and references to D. Abels, DO, Chairman, Recruiting Committee or Richard Mills, Executive Director, Memorial Hospital of Carbon County, Rawlins, WY 82301; (307) 324-2221.

NEUROLOGIST. Visalia Medical Clinic, Inc, a 37 physician multispecialty group, is searching for a Neurologist to enter an active practice. Located in the San Joaquin Valley in California and serving a market area of approximately 350,000. Excellent hospital services and facilities. BC/BE. Compensation is incentive oriented with rapid advancement to full partnership. Excellent fringe benefits. Please respond to John G. Heinsohn, Administrator, 5400 W. Hillsdale, Visalia, CA 93291; (209) 733-5222.

BEAUTIFUL COLORADO—Family Practice, Internal Medicine, and Occupational Physicians. Send CV to D. A. Franklin, MD, Medical Director, HealthWatch Medical Centers, 3400 Industrial Lane, Ste A, Broomfield, CO 80020.

PHYSICIANS WANTED

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Primary care physicians needed to work as *locum tenens* throughout California. High salary, paid malpractice. Work whenever you like. Permanent placements as well. Contact: Carol Sweig, Director, northern California, (415) 673-7676; Valerie Oblath, Director, southern California, (800) 437-7676.

Western Physicians Registry
710 Van Ness Ave
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DERMATOLOGIST. Visalia Medical Clinic has an opening for a BC/BE Dermatologist now staffed by one physician who has been with the Clinic for 15 years. Located in the San Joaquin Valley in central California and population approximately 350,000. Progressive city of 62,000, near national parks and the ocean. Compensation is incentive oriented with advancement to full partnership after one year. Excellent fringe benefits. If interested, CV to John G. Heinsohn, Administrator, 5400 W. Hillsdale, Visalia, CA 93291; (209) 733-5222.

NEUROSURGERY. Visalia Medical Clinic has an opening for a BC/BE Neurological Surgeon to enter an immediate and active practice. Located in the San Joaquin Valley of California, serving a market area of approximately 350,000 citizens. Two Neurosurgeons presently serving this area. Excellent hospital services and facilities. Must be BC/BE. Compensation is incentive oriented with advancement to full partnership after one year. Excellent fringe benefits. John G. Heinsohn, Administrator, 5400 W. Hillsdale, Visalia, CA 93291; (209) 733-5222.

OB/GYN. Multispecialty group in northwest Washington desires second Obstetrician. Excellent practice opportunity, full range of benefits, early partnership status, all practice costs paid. For more information contact Shane Spray, Administrator, 1400 E. Kincaid, Mount Vernon, WA 98273; (206) 428-2524.

FAMILY PRACTICE in four season playground. Live, work, and play in beautiful north Idaho. Excellent professional opportunity. Private practice affiliated with JCAH accredited hospital. For details call Nancy collect at (208) 784-1221, ext 304. Shoshone Medical Center, Jacobs Gulch, Kellogg, ID 83837.

PHYSICIANS WANTED

CHAIRMAN, DEPARTMENT OF INTERNAL MEDICINE, KERN MEDICAL CENTER. A county operated teaching hospital is seeking a chairman for this UCLA affiliated department. The department has nine full-time and part-time members, 18 residency positions all currently filled with quality graduates. Qualifications: BC in Internal Medicine, established record of scholarly achievement in teaching and patient care, demonstrated management skills to direct a fully accredited residency program in an active public hospital and relate to other programs at Kern Medical Center and the UCLA system. Candidate must be eligible for appointment to senior faculty position at UCLA and be licensed in the State of California. (The County of Kern is an Equal Opportunity Employer.) Address inquiries with CV to Paul Toot, MD, Chairman, Internal Medicine Search Committee, Kern Medical Center, 1830 Flower St, Bakersfield, CA 93305.

CALIFORNIA. Emergency Medicine Faculty Positions. Immediate opportunities available for career-oriented Emergency Physicians who possess excellent clinical and teaching skills to join the faculty of Emergency Medicine department. BC in Family Practice, Internal Medicine, Surgery, and/or BE in Emergency Medicine. Our facility, located in southern California, averages 38,000 Emergency department visits per year, is a level II trauma center, regional burn center and neonatology intensive care center. These positions require a teaching commitment in a university-affiliated Family Practice training program. We offer a competitive remuneration package to include salary, malpractice insurance, time off, and flexible scheduling. Send CV to Empire Medical Group, PO Box 3571, San Bernardino, CA 92413.

INTERNIST NEEDED FULL-TIME. Primary Care position for Board certified Internist is now available with a growing San Francisco Health Plan. The position includes both inpatient and outpatient responsibilities. Send CV to Medical Director, French Health Plan, 4131 Geary Blvd, San Francisco, CA 94118.

BROOKINGS, OREGON. Evening and weekend clinic. Family practice or emergency experience preferred. $35 per hour. Send CV to Art B. Wong, MD, FACEP, Emergency Physicians' Medical Group, 1 Maritime Plaza, Ste 710, San Francisco, CA 94111.

THE IRVINE MEDICAL CENTER AND THE UNIVERSITY OF CALIFORNIA-IRVINE, DEPARTMENT OF RADIOLOGICAL SCIENCES are seeking a full-time faculty member for the Department of Radiological Sciences at the Clinical Associate Professor or Clinical Professor level who would be assigned as Director of the Department of Radiology at Irvine Medical Center. The Irvine Medical Center is a new 177-bed hospital currently under construction in Irvine, California. Hospital opening is scheduled for fall of 1988. Administrative experience and academic background, including teaching and/or research, is required. Please send CV and the names of five references to Richard M. Friedenberg, MD, Professor and Chairman, Department of Radiological Sciences, University of California, Irvine, 101 City Drive South, Orange, CA 92668. The University of California is an Affirmative Action and an Equal Opportunity Employer.

FAMILY PRACTITIONER. Visalia Medical Clinic has an opening for a BC/BE Family Practitioner to join a four physician department. Located in the San Joaquin Valley of California, serving a market area of approximately 350,000 citizens, the Visalia Medical Clinic is a 40 physician multispecialty clinic. Excellent hospital services and facilities. Compensation is incentive oriented with advancement to full partnership after one year. Excellent fringe benefits. John G. Heinsohn, Administrator, 5400 W. Hillsdale, Visalia, CA 93291; (209) 733-5222.

(Continued on Page 250)

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AIR FORCE

(Continued from Page 248)

PHYSICIANS WANTED

DO YOU WANT TO PRACTICE GOOD PSYCHIATRY IN A LOVELY SETTING WITHOUT ALL THE HASSLES?

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We are looking for clinically experienced and well-trained Psychiatrists to provide inpatient and aftercare services in a state financed hospital setting where the average stay is 30 days, where there are 50 new admissions a month, and where the usual census is 180 psychiatric patients.

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6. Two-college town in lovely mid-Nebraska setting. Housing and cost of living considerably below the national average.

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Werner M. Mendel, MD, Clinical Director and Clinical Professor
Hastings Regional Center, Hastings, NE 68901
Telephone: (402) 463-2471

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PHYSICIANS WANTED

CALIFORNIA, SAN FRANCISCO BAY AREA. Full-time career Emergency Physician wanted for high volume Emergency department. Emergency Medicine BC/BE mandatory to participate in a group of twenty full-time staff physicians seeing over 300 patients per day. Salaried position, excellent benefits include three weeks paid vacation, one week CME, paid malpractice, health and life insurance, corporate shareholdership in three years. Send CV or contact David Gallagher, MD, 27400 Hesperian Blvd, Hayward, CA 94545.

INTERNIST. To join two Primary Care Internists in private practice in beautiful far-northern California one hour below major center. Midway between Portland and San Francisco, we have a rural setting with sophisticated practice and excellent hospital facilities. Subspecialty interest desirable within primary care framework. Salary and benefits with partnership an early goal. CV and your interests to R. H. Alley, Jr, MD, 105 Oberlin Rd, Yreka, CA 96097.

ONCOLOGIST/INTERNIST. BC/BE to join 21 physician primary care and multispecialty group practice in beautiful Pacific Northwest setting. Reply to Shane Spray, 1400 E. Kincaid, Mount Vernon, WA 98273; (206) 428-2524.

ESTABLISHED BC FAMILY PRACTITIONER in south central Washington seeks BE/BC associate with OB interest. Practice in rural, family-oriented community serving area of 45,000. Income guarantee and assistance with relocation. Ski at White Pass. Fishing and other water sports on nearby Rimrock Lake and Columbia River. Contact PROSEARCH, 305 NE 102nd Ave, Portland, OR 97220; (503) 256-2070, ext 202.

BE/BC FAMILY PRACTICE physician wanted to join young successful BC Family Practitioner to start new group in northeastern Colorado community. Includes OB. Service area of 25,000. Generous first year income guarantee and assistance with relocation. Only one and one-half hours from Denver. Contact PROSEARCH, 305 NE 102nd Ave, Portland, OR 97220; (503) 256-2070, ext 202.

PEDIATRICIAN. Visalia Medical Clinic has an opening for a BC/BE Pediatrician to join a five physician department. Located in the San Joaquin Valley of California, serving a market area of approximately 350,000 citizens, the Visalia Medical Clinic is a 40 physician multispecialty clinic. Excellent hospital services and facilities. Compensation is incentive oriented with advancement to full partnership after one year. Excellent fringe benefits. Contact Dr. James Simpson, 5400 W. Hillsdale, Visalia, CA 93291; (209) 733-5222.

PHYSICIANS WANTED

PACIFIC NORTHWEST, NEAR EUGENE, OREGON. BE/BC Internist wanted to join Family Practice group. Share call with Internists. Minimum salary guarantee. Good schools/outdoor recreation; University of Oregon/cultural events within 30 minutes. Contact John Hoopes, Cottage Grove Hospital, 1340 Birch St, Cottage Grove, OR 97424; (503) 942-0511.

NEAR STANFORD. Six Internists, all subspecialty trained and members of clinical faculty at Stanford, interested in an Associate with subspecialty interest and training. Should be well grounded in Internal Medicine. Send CV to Dr Bigler, El Camino Internal Medical Group, 125 South Dr, Mountain View, CA 94040.

IDAHO. Family Practitioner with interest in OB wanted to join three Family Practitioners serving scenic northern Idaho community. Hospital provides complete assistance—office, salary, full benefits. BE/BC and cesarean section experience required. Enjoy outdoor recreation, rural lifestyle. Contact Jean Erickson, PROSEARCH, 305 NE 102nd Ave, Portland, OR 97220-4199; (503) 256-2070.

SOUTH CENTRAL WASHINGTON COMMUNITY seeks BE/BC Internist for solo practice. Share office space with two other physicians. First year income guarantee and other assistance. Great income potential for right candidate! Progressive 38-bed hospital has CT services. Excellent schools and recreation. Contact PROSEARCH, 305 NE 102nd Ave, Portland, OR 97220; (503) 256-4488.

CALIFORNIA CENTRAL VALLEY. Desire BC/BE Family Practitioner to join busy two man Family Practice. Easy drive to San Francisco or mountains. Growing area; city of 40,000; good schools. Guarantee plus benefits. Reply to Number 59, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

NORTHERN CALIFORNIA OB/GYN. Beautiful Marin County, California OB/GYN practice looking for BC/BE female/male OB/GYN who is interested in joining a busy and successful practice of two MDs, one midwife, and four NPs. Progressive, busy OB practice offering family centered maternity care. Pro-choice philosophy. Opportunity for university affiliation. Lovely physical facilities with potential for investment. Must be well trained, enjoy working hard, committed to women's health care and fun to work with. Compensation package with partnership available in one year. Six weeks time off each year. Send résumé to WHMA/NEB, PO Box 1773, Ross, CA 94957.

PHYSICIANS WANTED

BC/BE INTERNIST to associate with General Surgeon, OB/GYN, Pediatrician, Internist, and three FPs in well-established rural practice. Send CV to R. F. LeBlond, MD, Park Clinic, Box 1139, Livingston, MT 59047.

INTERNIST. Live in San Francisco and commute to nearby rural area for four two-night shifts per month in combined Internal Medicine/Emergency room practice. Four Internists currently working in stable group. Practice quality medicine in the country where you can make a greater impact and enjoy lots of free time wherever you like to live. 72k per year. Charles Rath, MD, 199 E. Webster St, Colusa, CA 95932; (916) 458-7739.

INTERNIST: SAN FRANCISCO. BC/BE Internist wanted to join primary care group in San Francisco. We are currently three doctors sharing call, wish a fourth to expand call schedule and purchase a well-established practice in our area from retiring Internist (former president of ASIM). Send résumé to John Pierce, MD, 3620 Army St, San Francisco, CA 94110, or call (415) 826-7577.

GENERAL INTERNIST needed for large hospital-based multispecialty clinic. University associated residency program. Attractive salary and complete benefit package. Pleasant setting. BC/BE. California license required. Contact Dennis L. Ostrem, MD, Chief Internal Medicine, The Permanente Medical Group, Inc, PO Box 254999, Sacramento, CA 95865-4999 or call (916) 973-5781. An Equal Opportunity Employer.

FAMILY PRACTICE PHYSICIANS. Immediate positions availabe for BE/BC Family Practice Physicians to join a growth-oriented southern California group with an expanding PCCM program. Daytime office practice only; no nights, weekends or Obstetrics. Full-time permanent positions with guaranteed incomes and paid malpractice. Send CV to Medical Director, PO Box 16027, Long Beach, CA 90806; or call (213) 590-9696.

NORTHERN SAN FRANCISCO BAY AREA: Seeking Physician BC/BE in Internal Medicine for Internist position in growing department. Kaiser Permanente Medical Center, 1550 Gateway Blvd, Fairfield, CA 94533; (707) 427-4200.

EMERGENCY GROUP seeking career oriented ACLS, ATLS physician for immediate opening. Moderate volume, income $120,000. Great outdoor activities including fishing, boating, skiing and sailing in south central Washington. Send CV to KEP, PO Box 6192, Kennewick, WA 99336; or call (509) 627-1798.

(Continued on Page 252)

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BuSpar® (buspirone HCl)

References: **1.** Newton RE *et al* A review of the side effect profile of buspirone *Am J Med* 1986; 80(3B) 17-21 **2.** Moskowitz H and Smiley A Effects of chronically administered buspirone and diazepam on driving-related skills performance *J Clin Psychiatry* 1982; 43(12,Sec 2) 45-55 **3.** Lader M Assessing the potential for buspirone dependence or abuse and effects of its withdrawal *Am J Med* 1987; 82(5A) 20-26

Contraindications: Hypersensitivity to buspirone

Warnings: The administration of BuSpar to a patient taking a monoamine oxidase inhibitor (MAOI) may pose a hazard. Since blood pressure has become elevated when BuSpar was administered concomitantly with an MAOI, such concomitant use is not recommended. BuSpar should not be employed in lieu of appropriate antipsychotic treatment.

Precautions: ***General***—*Interference with cognitive and motor performance:* Although buspirone is less sedating than other anxiolytics and does not produce significant functional impairment, its CNS effects in a given patient may not be predictable, therefore, patients should be cautioned about operating an automobile or using complex machinery until they are reasonably certain that buspirone does not affect them adversely. Although buspirone has not been shown to increase alcohol-induced impairment in motor and mental performance, it is prudent to avoid concomitant use with alcohol.

Potential for withdrawal reactions in sedative/hypnotic/anxiolytic drug dependent patients: Because buspirone will not block the withdrawal syndrome often seen with cessation of therapy with benzodiazepines and other common sedative/hypnotic drugs, before starting buspirone withdraw patients gradually from their prior treatment, especially those who used a CNS depressant chronically. Rebound or withdrawal symptoms may occur over varying time periods, depending in part on the type of drug and its elimination half-life. The withdrawal syndrome can appear as any combination of irritability, anxiety, agitation, insomnia, tremor, abdominal cramps, muscle cramps, vomiting, sweating, flu-like symptoms without fever, and occasionally, even as seizures.

Possible concerns related to buspirone's binding to dopamine receptors. Because buspirone can bind to central dopamine receptors, a question has been raised about its potential to cause acute and chronic changes in dopamine mediated neurological function (e.g., dystonia, pseudoparkinsonism, akathisia, and tardive dyskinesia). Clinical experience in controlled trials has failed to identify any significant neuroleptic-like activity, however, a syndrome of restlessness, appearing shortly after initiation of treatment, has been reported, the syndrome may be due to increased central noradrenergic activity or may be attributable to dopaminergic effects (ie, represent akathisia).

Information for Patients—Patients should be instructed to inform their physician about any medications, prescription or non-prescription, alcohol or drugs they are now taking or plan to take during treatment with buspirone, to inform their physician if they are pregnant, are planning to become pregnant, or become pregnant while taking buspirone, to inform their physician if they are breast feeding, and not to drive a car or operate potentially dangerous machinery until they experience how this medication affects them.

Drug Interactions—Concomitant use with other CNS active drugs should be approached with caution (see **Warnings**). Concomitant use with trazodone may have caused 3- to 6-fold elevations on SGPT (ALT) in a few patients. Buspirone does not displace tightly bound drugs like phenytoin, propranolol, and warfarin from serum proteins, but may displace less firmly bound drugs like digoxin.

Carcinogenesis, Mutagenesis, Impairment of Fertility—No evidence of carcinogenic potential was observed in rats or mice; buspirone did not induce point mutations, nor was DNA damage observed, chromosomal aberrations or abnormalities did not occur.

Pregnancy: Teratogenic Effects—Pregnancy Category B: Should be used during pregnancy only if clearly needed.

Nursing Mothers—Administration to nursing women should be avoided if clinically possible.

Pediatric Use—The safety and effectiveness have not been determined in individuals below 18 years of age.

Use in the Elderly—No unusual, adverse, age-related phenomena have been identified in elderly patients receiving a total, modal daily dose of 15 mg.

Use in Patients with Impaired Hepatic or Renal Function—Since buspirone is metabolized by the liver and excreted by the kidneys, it is not recommended in severe hepatic or renal impairment.

Adverse Reactions (See also Precautions): ***Commonly Observed***—The more commonly observed untoward events include dizziness, nausea, headache, nervousness, lightheadedness, and excitement.

Associated with Discontinuation of Treatment—The more common events causing discontinuation included, central nervous system disturbances (3.4%), primarily dizziness, insomnia, nervousness, drowsiness, lightheaded feeling, gastrointestinal disturbances (1.2%), primarily nausea, miscellaneous disturbances (1.1%), primarily headache and fatigue. In addition, 3.4% of patients had multiple complaints, none of which could be characterized as primary.

Incidence in Controlled Clinical Trials—Adverse events reported by 1% or more of 477 patients who received buspirone in four-week, controlled trials: *Cardiovascular:* Tachycardia/palpitations 1%. *CNS:* Dizziness 12%, drowsiness 10%, nervousness 5%, insomnia 3%, lightheadedness 3%, decreased concentration 2%, excitement 2%, anger/hostility 2%, confusion 2%, depression 2%. *EENT:* Blurred vision 2%. *Gastrointestinal:* Nausea 8%, dry mouth 3%, abdominal/gastric distress 2%, diarrhea 2%, constipation 1%, vomiting 1%. *Musculoskeletal:* Musculoskeletal aches/pains 1%. *Neurological:* Numbness 2%, paresthesia 1%, incoordination 1%, tremor 1%. *Skin:* Skin rash 1%. *Miscellaneous:* Headache 6%, fatigue 4%, weakness 2%, sweating/clamminess 1%.

Other Events Observed During the Entire Pre-marketing Evaluation—The relative frequency of all other undesirable events reasonably associated with the use of buspirone in approximately 3000 subjects who took multiple doses of the drug under well-controlled, open, and uncontrolled conditions is defined as follows: Frequent are those occurring in at least 1/100 patients, infrequent are those occurring in 1/100 to 1/1000 patients; and rare are those occurring in less than 1/1000 patients. *Cardiovascular*—frequent: nonspecific chest pain; infrequent: syncope, hypotension, hypertension; rare: cerebrovascular accident, congestive heart failure, myocardial infarction, cardiomyopathy, bradycardia. *Central Nervous System*—frequent: dream disturbances; infrequent: depersonalization, dysphoria, noise intolerance, euphoria, akathisia, tearfulness, loss of interest, disassociative reaction, hallucinations, suicidal ideation, seizures; rare: feelings of claustrophobia, cold intolerance, stupor, slurred speech, psychosis. *EENT*—frequent: tinnitus, sore throat, nasal congestion; infrequent: redness and itching of the eyes, altered taste, altered smell, conjunctivitis; rare: inner ear abnormality, eye pain, photophobia, pressure on eyes. *Endocrine*—rare: galactorrhea, thyroid abnormality. *Gastrointestinal*—infrequent: flatulence, anorexia, increased appetite, salivation, irritable colon, rectal bleeding; rare: burning of the tongue. *Genitourinary*—infrequent: urinary frequency, urinary hesitancy, menstrual irregularity and spotting, dysuria; rare: amenorrhea, pelvic inflammatory disease, enuresis, nocturia. *Musculoskeletal*—infrequent: muscle cramps, muscle spasms, rigid/stiff muscles, arthralgias. *Neurological*—infrequent: involuntary movements, slowed reaction time; rare: muscle weakness. *Respiratory*—infrequent: hyperventilation, shortness of breath, chest congestion; rare: epistaxis. *Sexual Function*—infrequent: decreased or increased libido; rare: delayed ejaculation, impotence. *Skin*—infrequent: edema, pruritus, flushing, easy bruising, hair loss, dry skin, facial edema, blisters; rare: acne, thinning of nails. *Clinical Laboratory*—infrequent: increases in hepatic aminotransferases (SGOT, SGPT); rare: eosinophilia, leukopenia, thrombocytopenia. *Miscellaneous*—infrequent: weight gain, fever, roaring sensation in the head, weight loss, malaise; rare: alcohol abuse, bleeding disturbance, loss of voice, hiccoughs.

Drug Abuse and Dependence: ***Controlled Substance Class***—Not a controlled substance.

Physical and Psychological Dependence—Buspirone has shown no potential for abuse or diversion and there is no evidence that it causes tolerance, or either physical or psychological dependence. However, since it is difficult to predict from experiments the extent to which a CNS active drug will be misused, diverted, and/or abused once marketed, physicians should carefully evaluate patients for a history of drug abuse and follow such patients closely, observing them for signs of buspirone misuse or abuse (e.g., development of tolerance, incrementation of dose, drug-seeking behavior).

Overdosage: ***Signs and Symptoms***—At doses approaching 375 mg/day the following symptoms were observed: nausea, vomiting, dizziness, drowsiness, miosis, and gastric distress. No deaths have been reported in humans either with deliberate or accidental overdosage.

Recommended Overdose Treatment—General symptomatic and supportive measures should be used along with immediate gastric lavage. No specific antidote is known and dialyzability of buspirone has not been determined.

For complete details, see Prescribing Information or consult your Mead Johnson Pharmaceuticals Representative.

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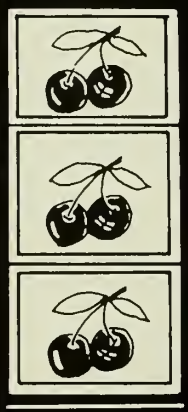

CLASSIFIED INFO (415) 882-5178

(Continued from Page 250)

PHYSICIANS WANTED

GASTROENTEROLOGIST—BC/BE to join two Gastroenterologists in busy private clinical practice located in highly desirable Los Angeles suburb. Strong clinical and endoscopic skills needed. We perform all diagnostic and therapeutic procedures including Laser and Sphincterotomy. Competitive salary and benefits with early partnership potential. Available July 1988 or sooner. Send CV to Number 80, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

UNIVERSITY OF CALIFORNIA, Irvine, Department of Medicine is seeking a full-time faculty person as General Internist for expanding academic group practice. Combined fee-for-service/capitation. Duties include 80-90% clinical practice in multispecialty faculty clinic, 10-20% teaching residents and students ambulatory care and inpatient medicine. Division of General Internal Medicine with strong commitment to teaching, practice, and research. Competitive salary and benefits. Affirmative action/equal opportunity employer. Send CV to Jeremiah Tilles, MD, UCI, Department of Medicine, Route 81, 101 City Drive South, Orange, CA 92668.

FAMILY PHYSICIANS, BC/BE, full- and part-time positions available with Obstetrics optional, to work with multispecialty group practice in the Seattle area. Attractive salary benefits. Contact Sharon Courlas, MD, (206) 326-4147. Send CV to Pacific Health Associates, 1200 12th Ave South, Seattle, WA 98144, Attn: Mary Anderson.

BC/BE INTERNIST. In northern California wine country. Join two man group in private practice of Internal Medicine. Subspecialty interest OK. Reply to Number 81, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

CRESCENT CITY, CALIFORNIA. Exciting position available at a growing 24,000-visit ER in a rural, coastal community. Fee-for-service with possibility of six figure income. Send CV to Art B. Wong, MD, FACEP, 1 Maritime Plaza, Ste 710, San Francisco, CA 94111.

GENERAL INTERNIST, BC/BE to join group practice in smaller community near Modesto, California. Join four other Internists and two Physicians Assistants. Full range of hospital and office practice. Must be interested in Primary Care focus, but will consider sub-specialty in Cardiology or Infectious Diseases. May call (collect) or write to Suzanne Meyer, MD, 6449 3rd St, Riverbank, CA 95367; (209) 869-6633.

EMERGENCY MEDICINE. We are an established 35-physician partnership in northern California and we are seeking BE/BC Emergency Physicians to join us. All of our facilities have moderate volumes, many serve as EMS base-stations. Salary and benefits are competitive; malpractice is paid. If interested in a career in Emergency Medicine with us, please contact Sacramento Emergency Medical Group, 4325 Auburn Blvd, Ste 100, Sacramento, CA 95841; (916) 486-4414.

CARDIOLOGIST. BC/BE sought to join a large hospital-based multispecialty clinic. University affiliated residency program. Excellent fringe benefits. Competitive salary. California license required. Send CV to Aung-Win Chiong, MD, The Permanente Medical Group, Inc, PO Box 254999, Sacramento, CA 95865-4999, or call (916) 973-5748. An Equal Opportunity Employer.

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(Continued on Page 257)

SPECIAL ISSUES

AIDS—A Global Perspective

The short and remarkable history of AIDS epidemiology began in 1981 with the description of the clinical syndrome in California and New York. In the 6 years that have followed, intensive epidemiologic studies have defined the mode of spread of AIDS and laid the foundation for current control efforts. Serosurveys and retrospective clinical studies have been used to trace the temporal origins of the pandemic prior to 1981, while prospective studies and an increasingly comprehensive worldwide surveillance system have provided more accurate data for the years following 1981. AIDS cases have now been reported and investigated throughout the world.

This issue, from the Special Programme on AIDS of the World Health Organization, considers the methods and limitations of AIDS case reporting and HIV serologic studies, summarizes modes of HIV transmission, defines geographic patterns of spread, and examines the epidemiology of HIV infections by continent.

—Jonathan M. Mann, MD
Director, Special Programme on AIDS
World Health Organization, Geneva

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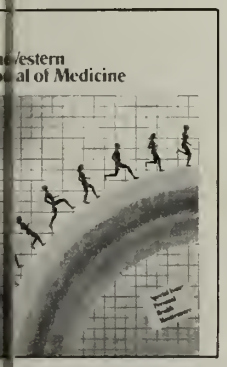

Personal Health Maintenance

The goal of this special issue is to provide an authoritative, current guide to disease prevention and health promotion. The contributors are distinguished experts in public health, epidemiology and clinical medicine.

—John H. Holbrook, MD

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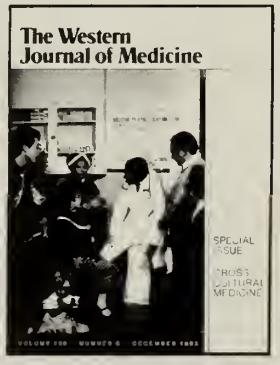

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—Malcolm S. M. Watts, MD

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See next page far references and Brief Summary of Praduct Informa-tian, which includes a listing of reported adverse reactions.

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TRANDATE® Tablets
(labetalol hydrochloride)

BRIEF SUMMARY OF PRODUCT INFORMATION

The following is a brief summary only. Before prescribing, see complete prescribing information in TRANDATE® Tablets product labeling.

INDICATIONS AND USAGE: TRANDATE® Tablets are indicated in the management of hypertension. TRANDATE Tablets may be used alone or in combination with other antihypertensive agents, especially thiazide and loop diuretics.

CONTRAINDICATIONS: TRANDATE® Tablets are contraindicated in bronchial asthma, overt cardiac failure, greater-than-first-degree heart block, cardiogenic shock, and severe bradycardia (see **WARNINGS**).

WARNINGS: Cardiac Failure: Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure. Beta-blockade carries a potential hazard of further depressing myocardial contractility and precipitating more severe failure. Although beta-blockers should be avoided in overt congestive heart failure, if necessary labetalol HCl can be used with caution in patients with a history of heart failure who are well compensated. Congestive heart failure has been observed in patients receiving labetalol HCl. Labetalol HCl does not abolish the inotropic action of digitalis on heart muscle.

In Patients Without a History of Cardiac Failure: In patients with latent cardiac insufficiency, continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or be given a diuretic, and the response should be observed closely. If cardiac failure continues despite adequate digitalization and diuretic, TRANDATE® therapy should be withdrawn (gradually, if possible).

Exacerbation of Ischemic Heart Disease Following Abrupt Withdrawal: Angina pectoris has not been reported upon labetalol HCl discontinuation. However, hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy; exacerbation of angina and, in some cases, myocardial infarction have occurred after *abrupt* discontinuation of such therapy. When discontinuing chronically administered TRANDATE, particularly in patients with ischemic heart disease, the dosage should be gradually reduced over a period of one to two weeks and the patient should be carefully monitored. If angina markedly worsens or acute coronary insufficiency develops, TRANDATE administration should be reinstituted promptly, at least temporarily, and other measures appropriate for the management of unstable angina should be taken. Patients should be warned against interruption or discontinuation of therapy without the physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue TRANDATE therapy abruptly even in patients treated only for hypertension.

Nonallergic Bronchospasm (eg, Chronic Bronchitis and Emphysema): Patients with bronchospastic disease should, in general, not receive beta-blockers. TRANDATE may be used with caution, however, in patients who do not respond to, or cannot tolerate, other antihypertensive agents. It is prudent, if TRANDATE is used, to use the smallest effective dose, so that inhibition of endogenous or exogenous beta-agonists is minimized.

Pheochromocytoma: Labetalol HCl has been shown to be effective in lowering blood pressure and relieving symptoms in patients with pheochromocytoma. However, paradoxical hypertensive responses have been reported in a few patients with this tumor; therefore, use caution when administering labetalol HCl to patients with pheochromocytoma.

Diabetes Mellitus and Hypoglycemia: Beta-adrenergic blockade may prevent the appearance of premonitory signs and symptoms (eg, tachycardia) of acute hypoglycemia. This is especially important with labile diabetics. Beta-blockade also reduces the release of insulin in response to hyperglycemia; it may therefore be necessary to adjust the dose of antidiabetic drugs.

Major Surgery: The necessity or desirability of withdrawing beta-blocking therapy prior to major surgery is controversial. Protracted severe hypotension and difficulty in restarting or maintaining a heartbeat have been reported with beta-blockers. The effect of labetalol HCl's alpha-adrenergic activity has not been evaluated in this setting.

A synergism between labetalol HCl and halothane anesthesia has been shown (see **Drug Interactions** under **PRECAUTIONS**).

PRECAUTIONS: General: *Impaired Hepatic Function:* TRANDATE® Tablets should be used with caution in patients with impaired hepatic function since metabolism of the drug may be diminished.

Jaundice or Hepatic Dysfunction: On rare occasions, labetalol HCl has been associated with jaundice (both hepatic and cholestatic). It is therefore recommended that treatment with labetalol HCl be stopped immediately should a patient develop jaundice or laboratory evidence of liver injury. Both have been shown to be reversible on stopping therapy.

Information for Patients: As with all drugs with beta-blocking activity, certain advice to patients being treated with labetalol HCl is warranted. This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects. While no incidence of the abrupt withdrawal phenomenon (exacerbation of angina pectoris) has been reported with labetalol HCl, dosing with TRANDATE Tablets should not be interrupted or discontinued without a physician's advice. Patients being treated with TRANDATE Tablets should consult a physician at any sign of impending cardiac failure. Also, transient scalp tingling may occur, usually when treatment with TRANDATE Tablets is initiated (see **ADVERSE REACTIONS**).

Laboratory Tests: As with any new drug given over prolonged periods, laboratory parameters should be observed over regular intervals. In patients with concomitant illnesses, such as impaired renal function, appropriate tests should be done to monitor these conditions.

Drug Interactions: In one survey, 2.3% of patients taking labetalol HCl in combination with tricyclic antidepressants experienced tremor as compared to 0.7% reported to occur with labetalol HCl alone. The contribution of each of the treatments to this adverse reaction is unknown, but the possibility of a drug interaction cannot be excluded.

Drugs possessing beta-blocking properties can blunt the bronchodilator effect of beta-receptor agonist drugs in patients with bronchospasm; therefore, doses greater than the normal antiasthmatic dose of beta-agonist bronchodilator drugs may be required.

Cimetidine has been shown to increase the bioavailability of labetalol HCl. Since this could be explained either by enhanced absorption or by an alteration of hepatic metabolism of labetalol HCl, special care should be used in establishing the dose required for blood pressure control in such patients.

Synergism has been shown between halothane anesthesia and intravenously administered labetalol HCl. During controlled hypotensive anesthesia using labetalol HCl in association with halothane, high concentrations (3% or above) of halothane should not be used because the degree of hypotension will be increased and because of the possibility of a large reduction in cardiac output and an increase in central venous pressure. The anesthesiologist should be informed when a patient is receiving labetalol HCl.

Labetalol HCl blunts the reflex tachycardia produced by nitroglycerin without preventing its hypotensive effect. If labetalol HCl is used with nitroglycerin in patients with angina pectoris, additional antihypertensive effects may occur.

Drug/Laboratory Test Interactions: The presence of a metabolite of labetalol in the urine may result in falsely increased levels of urinary catecholamines when measured by a nonspecific trihydroxyindole (THI) reaction. In screening patients suspected of having a pheochromocytoma and being treated with labetalol HCl, specific radioenzymatic or high performance liquid chromatography assay techniques should be used to determine levels of catecholamines or their metabolites.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term oral dosing studies with labetalol HCl for 18 months in mice and for two years in rats showed no evidence of carcinogenesis. Studies with labetalol HCl using dominant lethal assays in rats and mice and exposing microorganisms according to modified Ames tests showed no evidence of mutagenesis.

Pregnancy: ***Teratogenic Effects: Pregnancy Category C:*** Teratogenic studies have been performed with

TRANDATE® Tablets (labetalol hydrochloride)

labetalol in rats and rabbits at oral doses up to approximately six and four times the maximum recommended human dose (MRHD), respectively. No reproducible evidence of fetal malformations was observed. Increased fetal resorptions were seen in both species at doses approximating the MRHD. There are no adequate and well-controlled studies in pregnant women. Labetalol should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects: Infants of mothers who were treated with labetalol HCl during pregnancy did not appear to be adversely affected by the drug. Oral administration of labetalol to rats during late gestation through weaning at doses of two to four times the MRHD caused a decrease in neonatal survival.

Labor and Delivery: Labetalol HCl given to pregnant women with hypertension did not appear to affect the usual course of labor and delivery.

Nursing Mothers: Small amounts of labetalol (approximately 0.004% of the maternal dose) are excreted in human milk. Caution should be exercised when TRANDATE Tablets are administered to a nursing woman.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: Most adverse effects are mild, transient, and occur early in the course of treatment. In controlled clinical trials of three to four months' duration, discontinuation of TRANDATE® Tablets due to one or more adverse effects was required in 7% of all patients. In these same trials, beta-blocker control agents led to discontinuation in 8% to 10% of patients, and a centrally acting alpha-agonist in 30% of patients.

The following adverse reactions were derived from multi-center, controlled clinical trials over treatment periods of three and four months. The rates, which ranged from less than 1% to 5% except as otherwise noted, are based on adverse reactions considered probably drug-related by the investigator. If all reports are considered, the rates are somewhat higher (eg, dizziness, 20%; nausea, 14%; fatigue, 11%).

Body as a Whole: Fatigue, asthenia, and headache.

Gastrointestinal: Nausea (6%), vomiting, dyspepsia, diarrhea, and taste distortion.

Central and Peripheral Nervous Systems: Dizziness (11%), paresthesia, and drowsiness.

Autonomic Nervous System: Nasal stuffiness, ejaculation failure, impotence, and increased sweating.

Cardiovascular: Edema and postural hypotension.

Respiratory: Dyspnea.

Skin: Rash.

Special Senses: Vision abnormality and vertigo.

The adverse effects were reported spontaneously and are representative of the incidence of adverse effects that may be observed in a properly selected hypertensive patient population, ie, a group excluding patients with bronchospastic disease, overt congestive heart failure, or other contraindications to beta-blocker therapy.

Clinical trials also included studies utilizing daily doses up to 2,400 mg in more severely hypertensive patients. The US therapeutic trials data base for adverse reactions that are clearly or possibly dose-related shows that the following side effects increased with increasing dose: dizziness, fatigue, nausea, vomiting, dyspepsia, paresthesia, nasal stuffiness, ejaculation failure, impotence, and edema.

In addition, a number of other less common adverse events have been reported in clinical trials or the literature:

Cardiovascular: Postural hypotension, including rarely, syncope.

Central and Peripheral Nervous Systems: Paresthesias, most frequently described as scalp tingling. In most cases, it was mild, transient, and usually occurred at the beginning of treatment.

Collagen Disorders: Systemic lupus erythematosus; positive antinuclear factor (ANF).

Eyes: Dry eyes.

Immunological System: Antimitochondrial antibodies.

Liver and Biliary System: Cholestasis with or without jaundice.

Musculoskeletal System: Muscle cramps; toxic myopathy.

Respiratory System: Bronchospasm.

Skin and Appendages: Rashes of various types, such as generalized maculopapular, lichenoid, urticarial, bullous lichen planus, psoriaform, and facial erythema; Peyronie's disease; reversible alopecia.

Urinary System: Difficulty in micturition, including acute urinary bladder retention.

Following approval for marketing in the United Kingdom, a monitored release survey involving approximately 6,800 patients was conducted for further safety and efficacy evaluation of this product. Results of this survey indicate that the type, severity, and incidence of adverse effects were comparable to those cited above.

Potential Adverse Effects: In addition, other adverse effects not listed above have been reported with other beta-adrenergic blocking agents.

Central Nervous System: Reversible mental depression progressing to catatonia, an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance or neuropsychometrics.

Cardiovascular: Intensification of AV block (see **CONTRAINDICATIONS**).

Allergic: Fever combined with aching and sore throat; laryngospasm; respiratory distress.

Hematologic: Agranulocytosis; thrombocytopenic or nonthrombocytopenic purpura.

Gastrointestinal: Mesenteric artery thrombosis; ischemic colitis.

The oculomucocutaneous syndrome associated with the beta-blocker practolol has not been reported with labetalol HCl.

Clinical Laboratory Tests: There have been reversible increases of serum transaminases in 4% of patients treated with labetalol HCl and tested, and more rarely, reversible increases in blood urea.

OVERDOSAGE: Information concerning possible overdosage and its treatment appears in the full prescribing information.

DOSAGE AND ADMINISTRATION: DOSAGE MUST BE INDIVIDUALIZED. The recommended *initial* dosage is 100 mg *twice* daily whether used alone or added to a diuretic regimen. After two or three days, using standing blood pressure as an indicator, dosage may be titrated in increments of 100 mg bid every two or three days. The usual *maintenance* dosage of labetalol HCl is between 200 and 400 mg *twice* daily. Before use, see complete prescribing information for dosage details.

HOW SUPPLIED: TRANDATE® Tablets, 100 mg, light orange, round, scored, film-coated tablets engraved on one side with "TRANDATE 100 GLAXO," bottles of 100 (NDC 0173-0346-43) and 500 (NDC 0173-0346-44) and unit dose packs of 100 tablets (NDC 0173-0346-47).

TRANDATE Tablets, 200 mg, white, round, scored, film-coated tablets engraved on one side with "TRANDATE 200 GLAXO," bottles of 100 (NDC 0173-0347-43) and 500 (NDC 0173-0347-44) and unit dose packs of 100 tablets (NDC 0173-0347-47).

TRANDATE Tablets, 300 mg, peach, round, scored, film-coated tablets engraved on one side with "TRANDATE 300 GLAXO," bottles of 100 (NDC 0173-0348-43) and 500 (NDC 0173-0348-44) and unit dose packs of 100 tablets (NDC 0173-0348-47).

TRANDATE Tablets should be stored between 2° and 30°C (36° and 86°F). TRANDATE Tablets in the unit dose boxes should be protected from excessive moisture.

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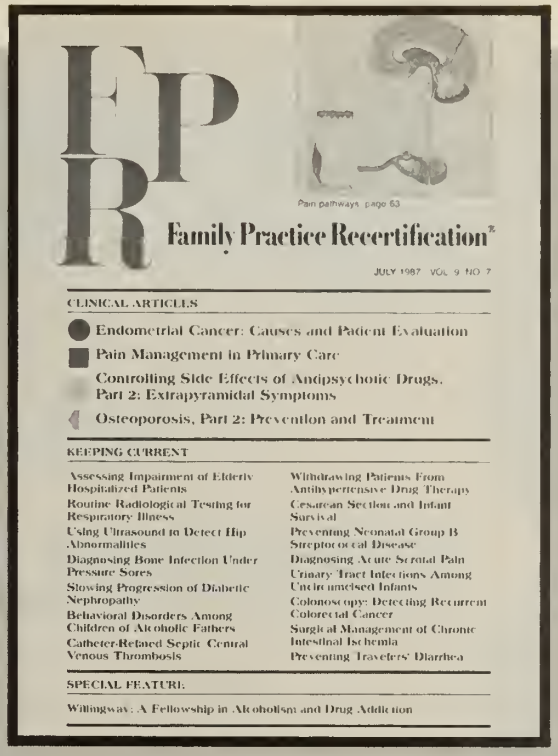
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(Continued from Page 252)

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INTERNIST. Immediate opening for a BC/BE General Internist to join a 35-member multispecialty group located in San Luis Obispo on the central coast. Benefits include immediate shareholder status, retirement program, all practice costs paid, starting guaranteed salary plus strong incentive plan. Send CV to Recruitment, San Luis Medical Clinic, Ltd., 1235 Osos St, San Luis Obispo, CA 93401-3619.

OREGON. Family Practice Physician partner needed for immediate care center and private practice in recreational Oregon paradise. No start-up costs, thriving practice, and generous free time to spend skiing or hiking the mountains or on the river, enjoying some of the best windsurfing waters in the world. Located in Hood River which offers the peace and quiet of a small community, yet is only an hour away from the culture and activity of Oregon's largest metropolitan area. Contact John Jacobson, MD, Medical Director, Care Corner, 1151 May St, Hood River, OR 97031; (503) 386-1111 (collect).

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THREE FULL-TIME GENERAL INTERNISTS are being recruited for positions in the Division of General Medicine, Department of Internal Medicine, University of New Mexico School of Medicine. Primary responsibilities include inpatient and outpatient care and teaching. Applicants with subspecialty training will be considered. Applicants must be BC/BE. Faculty appointment based on academic credentials and experience. Please send inquiries and résumé/CV to Pat Cleve, Department of Medicine, University of New Mexico, Albuquerque, NM 87131.

INTERNIST BC/BE to join Internist/Cardiologist in central California near Fresno. Reply to Number 85, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

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CARDIOLOGIST. Columbus Hospital in Great Falls, Montana, has an immediate need for a BE/BC, invasive/non-invasive Cardiologist. At the foot of the eastern slopes of the Rockies, Great Falls is best known for its accessibility to superb recreational activities—skiing, fishing, hunting, camping, hiking, back-packing, etc. With excellent school systems and a very moderate cost of living, Great Falls has an excellent overall quality of life. Opportunity offers a guaranteed income plus incentives. Please send CV to Charles Matenaer, PRM, Inc, 15975 W. National Ave, New Berlin, WI 53151, or call (414) 784-2777.

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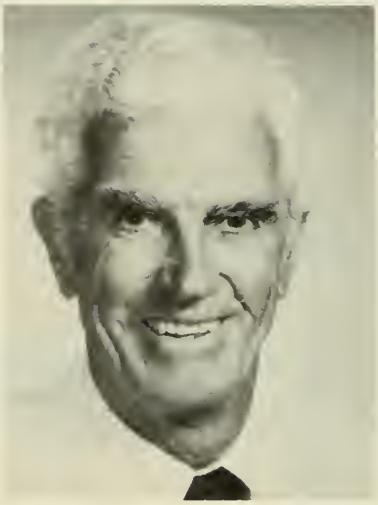

Telfer B. Reynolds, MD/Golden Apple Award

Telfer B. Reynolds, MD, Clayton G. Loosli Professor of Medicine at the University of Southern California, has been selected by the Committee on Scientific Assemblies to receive CMA's 1988 Golden Apple Award. This award spotlights exceptional physician speakers who have made a lifelong commitment to teaching and become distinguished by their charismatic, scientific and educational talents.

California Medical Association's 1988 Western Scientific Assembly will be held March 4-6 at Reno-Sparks Convention Center. Persons attending scientific courses or special conferences are asked to register on site in the North Hall Concourse of the convention center. For more information on the following programs please contact CMA at (415) 541-0900.

FRIDAY, MARCH 4

- ❑ Basic Cardiac Life Support Workshop
- ❑ AIDS—What the Practicing Physican Should Know in 1988
- ❑ Techniques & Problems in Handling Hazardous Material Disasters
- ❑ Sleep Disorders
- ❑ Symposium on Developmental Disabilities
- ❑ Pulmonary Medicine Update
- ❑ Neurosurgery in the Aging Population
- ❑ Golden Apple Award: Telfer B. Reynolds, MD

SATURDAY, MARCH 5

- ❑ Advanced Cardiac Life Support: Certification Course
- ❑ Cardiovascular Risk-Assessment and Intervention in Primary Care
- ❑ What's Allergy, What's Not: Common Health Problems in the Workplace
- ❑ Implantable Electromagnetic Hearing Device
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- ❑ Hair Symposium—Answer Your Patients' Questions
- ❑ Update on Gynecologic Cancer Screening
- ❑ It's A Wilderness Out There! Medical Emergencies of the Great Outdoors
- ❑ Opthalmology in the Year 2001
- ❑ Colorectal Carcinoma: Update 1988
- ❑ Family Crisis of the 1980's: Alcohol and Drug Abuse
- ❑ Eye Care in the Elderly
- ❑ The Impaired Doctor

Western Scientific Assembly

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SATURDAY, MARCH 5

- ❑ Skin Cancer: Everyone's Problem
- ❑ The Neuropsychiatrically Impaired Physician
- ❑ Marketing Roundtable 1988
- ❑ Roberta F. Fenlon Memorial Lecture: Dame Sheila Sherlock

SUNDAY, MARCH 6

- ❑ Advanced Cardiac Life Support: Certification/Recertification Course
- ❑ What the Non-Urologist Should Know About Urology in '88
- ❑ Recognition of Premalignant and Precursor Lesions of the Skin and Genitalia
- ❑ Suture Course
- ❑ Adolescent Psychological Problems
- ❑ Seminars in Orthopaedic Management
- ❑ What Every Computer Illiterate Should Know
- ❑ Consulting with the Anesthesiologist
- ❑ A Critical Look at the Washington Scene
- ❑ Public Health and Policy: AIDS in California 1988
- ❑ Physician and the Law—1988
- ❑ Keynote Speaker: Robert S. Eliot, MD, FACC

The Western Scientific Assembly

CONCURRENT EVENTS

HOUSE OF DELEGATES

The CMA House of Delegates meets Saturday, March 5 through Wednesday, March 9 at Bally's Hotel. Sit in on reference committee hearings and House sessions to see firsthand how CMA policies are shaped. Highlights of this year's House will be the farewell address of out-going CMA President Dr. Frederick S. Armstrong, a San Jose internist, and the inaugural address of CMA's President-Elect, Dr. Laurens P. White, a San Francisco internist specializing in oncology. Registration will be available March 3-9 at Bally's Hotel in the Grand Salon.

HOSPITAL MEDICAL STAFF SECTION ANNUAL ASSEMBLY

The CMA-HMSS Annual Assembly will be Friday, March 5 at Bally's Hotel. Included will be their keynote speaker, Kenneth Nelson, MD, "The View from Here—the PRO Sanction Process."

SPECIAL EVENTS

A variety of special tours will be offered this year. Registration takes place at the Reno-Sparks Convention Center.

- ❑ Reno City Gaming Tour
- ❑ Virginia City Tour
- ❑ Lake Tahoe Cruise
- ❑ Western Hoe-Down and Harrah's Classic Auto Tour
- ❑ Pre and Post Convention Ski Packages: Ski Lake Tahoe

EXHIBITS

The exhibit hall at Reno-Sparks Convention Center offers something for everyone: pharmaceuticals, educational displays, computer and office systems, medical testing systems, insurance, investment opportunities, health and home helps. Prizes!

GENERAL INFORMATION

LOCATION

The CMA 1988 Western Scientific Assembly will be held at the Reno-Sparks Convention Center, 4590 S. Virginia Street, Reno, Nevada, 89502. The House of Delegates will be headquartered in the Bally's Reno Hotel, 2500 E. Second Street, Reno, Nevada, 89595. Call (702) 789-2033 for hotel reservation information.

FEES

There is no charge to CMA members and their non-physician family members for general registration, nor to registered nurses, residents, interns or medical students. A general registration fee of $150 is charged to non-member physicians.

REGISTRATION

Advance registration closes February 12, 1988. Attendees may register on site at the Reno/Sparks Convention Center or Bally's Reno Hotel. Registration will be open:

Thursday, March 3	
1-5 pm	Bally's Hotel, Grand Salon
Friday, March 4	
7:30 am-5 pm	Bally's Hotel, Grand Salon
7 am-5 pm	Convention Center
Saturday, March 5	
7 am-5 pm	Bally's Hotel, Grand Salon
7 am-5 pm	Convention Center
Sunday, March 6	
7:30 am-5 pm	Bally's Hotel, Grand Salon
7 am-5 pm	Convention Center

SHUTTLE BUS SERVICE

Shuttle service from Bally's Hotel to Reno-Sparks Convention Center (located 3 miles away) will be continuous from 6:30 am to 7:30 pm.

ANY QUESTIONS?

Call CMA, (415) 541-0900

(Continued from Page 257)

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(Continued on Page 264)

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Arizona Medical Association, Inc—810 W Bethany Home Rd, Phoenix 85013. (602) 246-8901. Annual Meeting: June 9-11, 1988, Loew's Ventana Canyon Resort, Tucson.

California Medical Association—PO Box 7690, San Francisco 94120-7690. (415) 541-0900. Annual Meeting: March 4-9, 1988, Bally's Grand Hotel, Reno.

Colorado Medical Society—PO Box 17550, Denver 80217-0550. (303) 779-5455. Annual Meeting: September 15-17, 1988, Marriott City Center, Denver.

Hawaii Medical Association—320 Ward Ave, Suite 200, Honolulu 96814. (808) 536-7702. Annual Meeting: October 10-12, 1987, Kauai Surf, Kauai.

Idaho Medical Association—305 W Jefferson, PO Box 2668, Boise 83701. (208) 344-7888. Annual Meeting: July 21-23, 1988, Sun Valley.

Montana Medical Association—2012 11th Ave, Suite 12, Helena 59601. (406) 443-4000. Annual Meeting: September 29-October 1, 1988, Heritage Inn, Great Falls.

Nevada State Medical Association—3660 Baker Lane, Reno 89502. (702) 825-6788. Annual Meeting: April 21-24, 1988, Laughlin.

New Mexico Medical Society—303 San Mateo NE, Suite 204, Albuquerque 87108. (505) 266-7868. Annual Meeting: May 5-7, 1988, Hilton Inn, Albuquerque.

Oregon Medical Association—5210 SW Corbett Ave, Portland 97201. (503) 226-1555. Annual Meeting: (House of Delegates only): November 6-8, 1987, Portland.

Utah Medical Association—540 E Fifth South, Salt Lake City 84102. (801) 355-7477. Annual Meeting: September 21-23, 1988, University Park Hotel, Salt Lake City.

Washington State Medical Association—900 United Airlines Bldg, 2033 6th Ave, Seattle 98121. (206) 441-WSMA. Annual Meeting: September 15-18, 1988, Yakima.

Wyoming Medical Society—PO Drawer 4009, Cheyenne 82003-4009. (307) 635-2424. Annual Meeting: June 23-26, 1988, Jackson Lake Lodge, Moran.

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BACTRIM™ (trimethoprim and sulfamethoxazole/Roche)

Before prescribing, please consult complete product information, a summary of which follows:

CONTRAINDICATIONS: Hypersensitivity to trimethoprim or sulfonamides; documented megaloblastic anemia due to folate deficiency, pregnancy at term and during the nursing period, infants less than two months of age

WARNINGS: FATALITIES ASSOCIATED WITH THE ADMINISTRATION OF SULFONAMIDES, ALTHOUGH RARE, HAVE OCCURRED DUE TO SEVERE REACTIONS, INCLUDING STEVENS-JOHNSON SYNDROME, TOXIC EPIDERMAL NECROLYSIS, FULMINANT HEPATIC NECROSIS, AGRANULOCYTOSIS, APLASTIC ANEMIA AND OTHER BLOOD DYSCRASIAS.

BACTRIM SHOULD BE DISCONTINUED AT THE FIRST APPEARANCE OF SKIN RASH OR ANY SIGN OF ADVERSE REACTION. Clinical signs, such as rash, sore throat, fever, pallor, purpura or jaundice, may be early indications of serious reactions In rare instances a skin rash may be followed by more severe reactions, such as Stevens-Johnson syndrome, toxic epidermal necrolysis, hepatic necrosis or serious blood disorder Perform complete blood counts frequently

BACTRIM SHOULD NOT BE USED IN THE TREATMENT OF STREPTOCOCCAL PHARYNGITIS Clinical studies show that patients with group A β-hemolytic streptococcal tonsillopharyngitis have a greater incidence of bacteriologic failure when treated with Bactrim than with penicillin

PRECAUTIONS: *General* Give with caution to patients with impaired renal or hepatic function, possible folate deficiency (e g , elderly, chronic alcoholics, patients on anticonvulsants, with malabsorption syndrome, or in malnutrition states) and severe allergies or bronchial asthma In glucose-6-phosphate dehydrogenase deficient individuals, hemolysis may occur, frequently dose-related

Use in the Elderly May be increased risk of severe adverse reactions in elderly, particularly with complicating conditions, e g , impaired kidney and/or liver function, concomitant use of other drugs Severe skin reactions, generalized bone marrow suppression (see WARNINGS and ADVERSE REACTIONS) or a specific decrease in platelets (with or without purpura) are most frequently reported severe adverse reactions in elderly In those concurrently receiving certain diuretics, primarily thiazides, increased incidence of thrombocytopenia with purpura reported Make appropriate dosage adjustments for patients with impaired kidney function (see DOSAGE AND ADMINISTRATION)

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Information for Patients Instruct patients to maintain adequate fluid intake to prevent crystalluria and stone formation.

Laboratory Tests Perform complete blood counts frequently, if a significant reduction in the count of any formed blood element is noted, discontinue Bactrim. Perform urinalyses with careful microscopic examination and renal function tests during therapy, particularly for patients with impaired renal function.

Drug Interactions In elderly patients concurrently receiving certain diuretics, primarily thiazides, an increased incidence of thrombocytopenia with purpura has been reported Bactrim may prolong the prothrombin time in patients who are receiving the anticoagulant warfarin Keep this in mind when Bactrim is given to patients already on anticoagulant therapy and reassess coagulation time Bactrim may inhibit the hepatic metabolism of phenytoin Given at a common clinical dosage, it increased the phenytoin half-life by 39% and decreased the phenytoin metabolic clearance rate by 27% When giving these drugs concurrently, be alert for possible excessive phenytoin effect Sulfonamides can displace methotrexate from plasma protein binding sites, thus increasing free methotrexate concentrations

Drug/Laboratory Test Interactions Bactrim, specifically the trimethoprim component, can interfere with a serum methotrexate assay as determined by the competitive binding protein technique (CBPA) when a bacterial dihydrofolate reductase is used as the binding protein No interference occurs if methotrexate is measured by a radioimmunoassay (RIA). The presence of trimethoprim and sulfamethoxazole may also interfere with the Jaffé alkaline picrate reaction assay for creatinine, resulting in overestimations of about 10% in the range of normal values

Carcinogenesis, Mutagenesis, Impairment of Fertility Carcinogenesis Long-term studies in animals to evaluate carcinogenic potential not conducted with Bactrim *Mutagenesis* Bacterial mutagenic studies not performed with sulfamethoxazole and trimethoprim in combination Trimethoprim demonstrated to be nonmutagenic in the Ames assay No chromosomal damage observed in human leukocytes *in vitro* with sulfamethoxazole and trimethoprim alone or in combination, concentrations used exceeded blood levels of these compounds following therapy with Bactrim Observations of leukocytes obtained from patients treated with Bactrim revealed no chromosomal abnormalities. *Impairment of Fertility* No adverse effects on fertility or general reproductive performance observed in rats given oral dosages as high as 70 mg/kg/day trimethoprim plus 350 mg/kg/day sulfamethoxazole

Pregnancy Teratogenic Effects Pregnancy Category C. Trimethoprim and sulfamethoxazole may interfere with folic acid metabolism, use during pregnancy only if potential benefit justifies potential risk to fetus. Nonteratogenic Effects See CONTRAINDICATIONS section

Nursing Mothers See CONTRAINDICATIONS section

Pediatric Use Not recommended for infants under two months (see INDICATIONS and CONTRAINDICATIONS sections).

ADVERSE REACTIONS: Most common are gastrointestinal disturbances (nausea, vomiting, anorexia) and allergic skin reactions (such as rash and urticaria) **FATALITIES ASSOCIATED WITH THE ADMINISTRATION OF SULFONAMIDES, ALTHOUGH RARE, HAVE OCCURRED DUE TO SEVERE REACTIONS, INCLUDING STEVENS-JOHNSON SYNDROME, TOXIC EPIDERMAL NECROLYSIS, FULMINANT HEPATIC NECROSIS, AGRANULOCYTOSIS, APLASTIC ANEMIA AND OTHER BLOOD DYSCRASIAS (SEE WARNINGS SECTION)**

Hematologic Agranulocytosis, aplastic anemia, thrombocytopenia, leukopenia, neutropenia, hemolytic anemia, megaloblastic anemia, hypoprothrombinemia, methemoglobinemia, eosinophilia *Allergic Reactions* Stevens-Johnson syndrome, toxic epidermal necrolysis, anaphylaxis, allergic myocarditis, erythema multiforme, exfoliative dermatitis, angioedema, drug fever, chills, Henoch-Schoenlein purpura, serum sickness-like syndrome, generalized allergic reactions, generalized skin eruptions, photosensitivity, conjunctival and scleral injection, pruritus, urticaria and rash Periarteritis nodosa and systemic lupus erythematosus have been reported. *Gastrointestinal* Hepatitis (including cholestatic jaundice and hepatic necrosis), elevation of serum transaminase and bilirubin, pseudomembranous enterocolitis, pancreatitis, stomatitis, glossitis, nausea, emesis, abdominal pain, diarrhea, anorexia *Genitourinary* Renal failure, interstitial nephritis, BUN and serum creatinine elevation, toxic nephrosis with oliguria and anuria, crystalluria *Neurologic* Aseptic meningitis, convulsions, peripheral neuritis, ataxia, vertigo, tinnitus, headache *Psychiatric* Hallucinations, depression, apathy, nervousness *Endocrine* Sulfonamides bear certain chemical similarities to some goitrogens, diuretics (acetazolamide and the thiazides) and oral hypoglycemic agents; cross-sensitivity may exist Diuresis and hypoglycemia have occurred rarely in patients receiving sulfonamides. *Musculoskeletal* Arthralgia, myalgia *Miscellaneous* Weakness, fatigue, insomnia.

DOSAGE AND ADMINISTRATION: Not recommended for use in infants less than two months of age.

URINARY TRACT INFECTIONS AND SHIGELLOSIS IN ADULTS AND CHILDREN, AND ACUTE OTITIS MEDIA IN CHILDREN *Usual adult dosage* for urinary tract infections is one DS tablet, two tablets or four teaspoonfuls (20 ml) *b.i.d.* for 10 to 14 days Use identical daily dosage for 5 days for shigellosis *Recommended dosage for children* with urinary tract infections or acute otitis media is 8 mg/kg trimethoprim and 40 mg/kg sulfamethoxazole per 24 hours, in two divided doses every 12 hours for 10 days Use identical daily dosage for 5 days for shigellosis. *Renal Impaired* Creatinine clearance above 30 ml/min, give usual dosage; 15-30 ml/min, give one-half the usual regimen; below 15 ml/min, use not recommended

ACUTE EXACERBATIONS OF CHRONIC BRONCHITIS IN ADULTS Usual adult dosage is one DS tablet, two tablets or four teasp. (20 ml) *b.i.d* for 14 days.

PNEUMOCYSTIS CARINII PNEUMONITIS Recommended dosage is 20 mg/kg trimethoprim and 100 mg/kg sulfamethoxazole per 24 hours in equal doses every 6 hours for 14 days. See complete product information for suggested children's dosage table

HOW SUPPLIED: *DS (double strength) Tablets* (160 mg trimethoprim and 800 mg sulfamethoxazole)—bottles of 100, 250 and 500; Tel-E-Dose® packages of 100; Prescription Paks of 20 *Tablets* (80 mg trimethoprim and 400 mg sulfamethoxazole)—bottles of 100 and 500. Tel-E-Dose® packages of 100; Prescription Paks of 40. *Pediatric Suspension* (40 mg trimethoprim and 200 mg sulfamethoxazole per teasp.)—bottles of 100 ml and 16 oz (1 pint) *Suspension* (40 mg trimethoprim and 200 mg sulfamethoxazole per teasp.)—bottles of 16 oz (1 pint)

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Please see references and summary of product information on following page.

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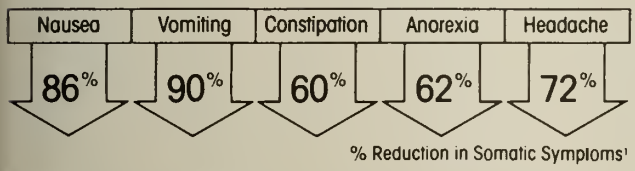

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Indications: Relief of moderate to severe depression associated with moderate to severe anxiety
Contraindications: Known hypersensitivity to benzodiazepines or tricyclic antidepressants. Do not use with manoamine oxidase (MAO) inhibitors or within 14 days following discontinuation of MAO inhibitors since hyperpyretic crises, severe convulsions and deaths have occurred with concomitant use; then initiate cautiously, gradually increasing dosage until optimal response is achieved. Contraindicated during acute recovery phase following myocardial infarction.
Warnings: Use with great care in patients with history of urinary retention or angle-closure glaucoma. Severe constipation may occur in patients taking tricyclic antidepressants and anticholinergic-type drugs. Closely supervise cardiovascular patients. (Arrhythmias, sinus tachycardia and prolongation of conduction time reported with use of tricyclic antidepressants, especially high doses. Myocardial infarction and stroke reported with use of this class of drugs.) Caution patients about possible combined effects with alcohol and other CNS depressants and against hazardous occupations requiring complete mental alertness (e.g., operating machinery, driving).

***Usage in Pregnancy:* Use of minor tranquilizers during the first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.**

Since physical and psychological dependence to chlordiazepoxide have been reported rarely, use caution in administering Limbitrol to addiction-prone individuals or those who might increase dosage; withdrawal symptoms following discontinuation of either component alone have been reported (nausea, headache and malaise for amitriptyline; symptoms [including convulsions] similar to those of barbiturate withdrawal for chlordiazepoxide).
Precautions: Use with caution in patients with a history of seizures, in hyperthyroid patients or those on thyroid medication, and in patients with impaired renal or hepatic function. Because of the possibility of suicide in depressed patients, do not permit easy access to large quantities in these patients. Periodic liver function tests and blood counts are recommended during prolonged treatment. Amitriptyline component may block action of guanethidine or similar antihypertensives. When tricyclic antidepressants are used concomitantly with cimetidine (Tagamet), clinically significant effects have been reported involving delayed elimination and increasing steady state concentrations of the tricyclic drugs. Concomitant use of Limbitrol with other psychotropic drugs has not been evaluated, sedative effects may be additive. Discontinue several days before surgery. Limit concomitant administration of ECT to essential treatment. See Warnings for precautions about pregnancy. Limbitrol should not be taken during the nursing period. Not recommended in children under 12. In the elderly and debilitated, limit to smallest effective dosage to preclude ataxia, oversedation, confusion or anticholinergic effects.
Adverse Reactions: Most frequently reported are those associated with either component alone: drowsiness, dry mouth, constipation, blurred vision, dizziness and bloating. Less frequently occurring reactions include vivid dreams, impotence, tremor, confusion and nasal congestion. Many depressive symptoms including anorexia, fatigue, weakness, restlessness and lethargy have been reported as side effects of both Limbitrol and amitriptyline. Granulocytopenia, jaundice and hepatic dysfunction have been observed rarely.
The following list includes adverse reactions not reported with Limbitrol but requiring consideration because they have been reported with one or both components or closely related drugs:
Cardiovascular: Hypotension, hypertension, tachycardia, palpitations, myocardial infarction, arrhythmias, heart block, stroke.
Psychiatric: Euphoria, apprehension, poor concentration, delusions, hallucinations, hypomania and increased or decreased libido.
Neurologic: Incoordination, ataxia, numbness, tingling and paresthesias of the extremities, extrapyramidal symptoms, syncope, changes in EEG patterns.
Anticholinergic: Disturbance of accommodation, paralytic ileus, urinary retention, dilatation of urinary tract.
Allergic: Skin rash, urticaria, photosensitization, edema of face and tongue, pruritus.
Hematologic: Bone marrow depression including agranulocytosis, eosinophilia, purpura, thrombocytopenia.
Gastrointestinal: Nausea, epigastric distress, vomiting, anorexia, stomatitis, peculiar taste, diarrhea, black tongue.
Endocrine: Testicular swelling and gynecomastia in the male, breast enlargement, galactorrhea and minor menstrual irregularities in the female, elevation and lowering of blood sugar levels, and syndrome of inappropriate ADH (antidiuretic hormone) secretion.
Other: Headache, weight gain or loss, increased perspiration, urinary frequency, mydriasis, jaundice, alopecia, parotid swelling.
Overdosage: Immediately hospitalize patient suspected of having taken an overdose. Treatment is symptomatic and supportive. I.V. administration of 1 to 3 mg physostigmine salicylate has been reported to reverse the symptoms of amitriptyline poisoning. See complete product information for manifestation and treatment.
Dosage: Individualize according to symptom severity and patient response. Reduce to smallest effective dosage when satisfactory response is obtained. Larger portion of daily dose may be taken at bedtime. Single *h.s.* dose may suffice for some patients. Lower dosages are recommended for the elderly. Limbitrol DS (double strength) Tablets, initial dosage of three or four tablets daily in divided doses, increased up to six tablets or decreased to two tablets daily as required. Limbitrol Tablets, initial dosage of three or four tablets daily in divided doses, for patients who do not tolerate higher doses.
How Supplied: *Double strength (DS) Tablets,* white, film-coated, each containing 10 mg chlordiazepoxide and 25 mg amitriptyline (as the hydrochloride salt), and *Tablets,* blue, film-coated, each containing 5 mg chlordiazepoxide and 12.5 mg amitriptyline (as the hydrochloride salt). Available in bottles of 100 and 500; Tel-E-Dose® packages of 100, Prescription Paks of 50.

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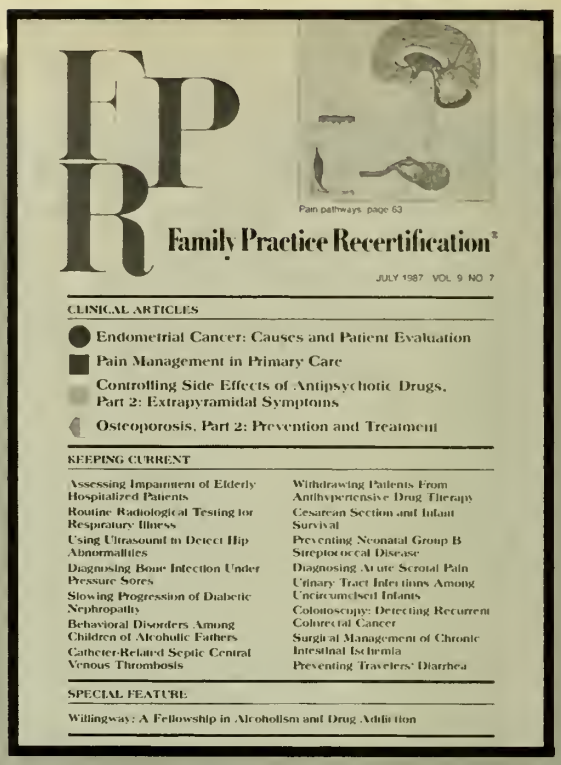
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Clinical Investigation—Papers that authors wish considered for the Clinical Investigation section should be so designated in the transmittal letter. Such papers should describe experimental work in humans that extensively and prospectively examines scientific hypotheses relating to disease.

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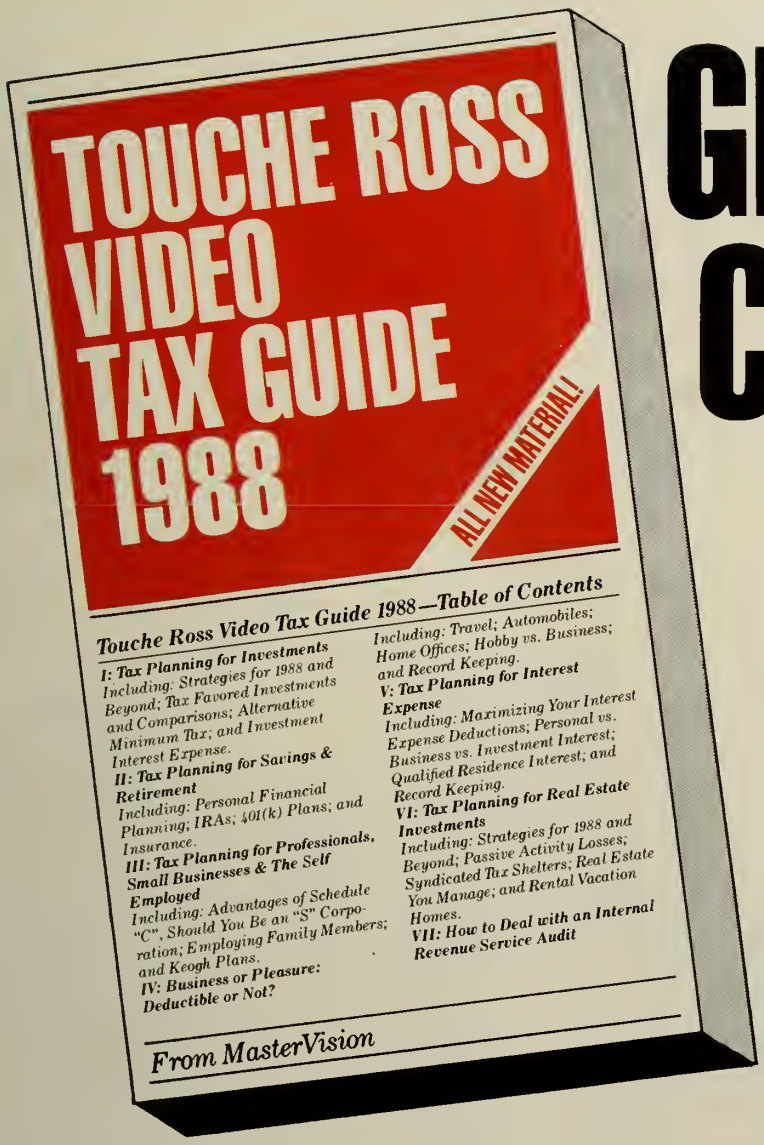

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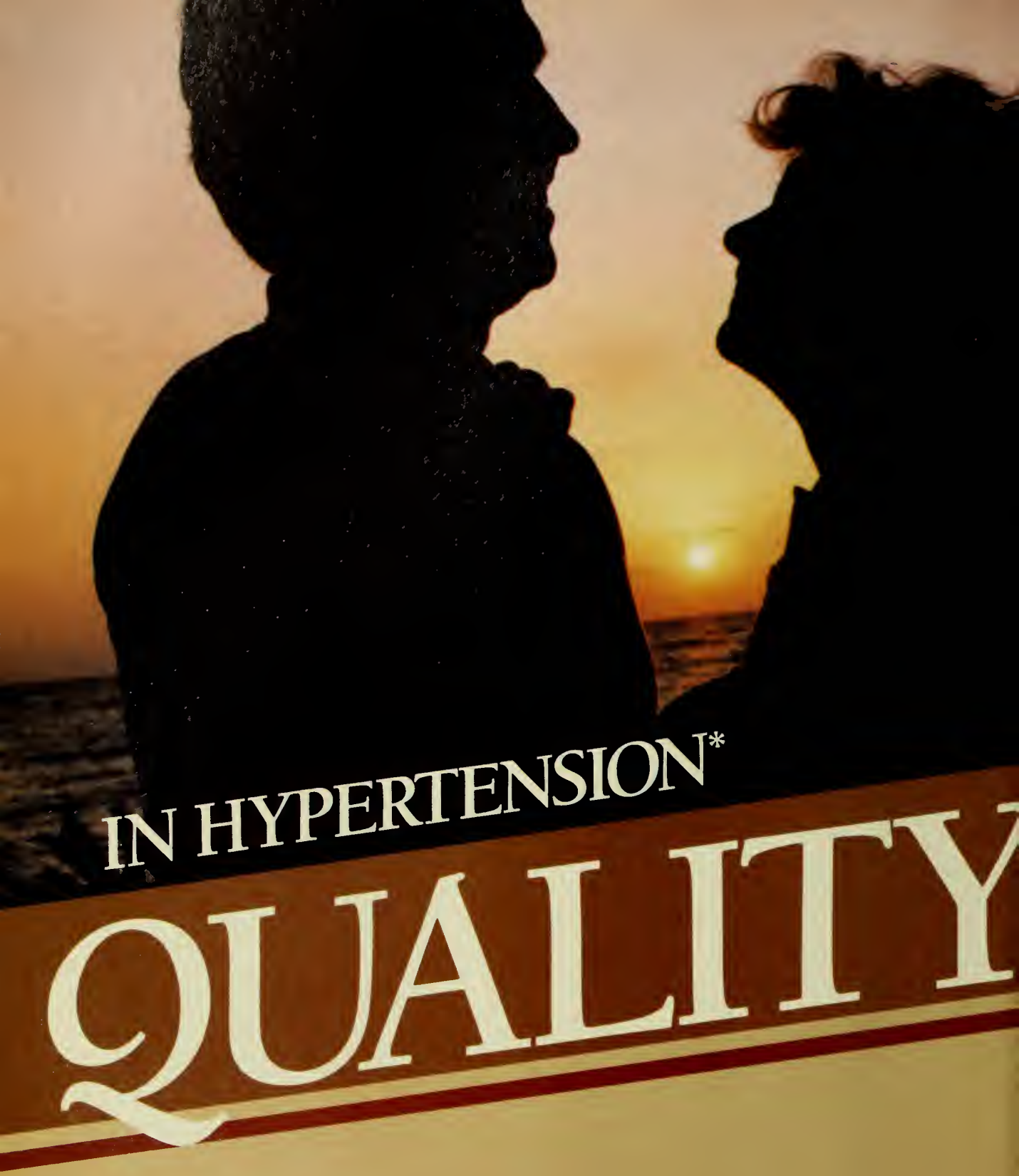

*CAPOTEN® (captopril tablets) may be used as initial therapy only for patients with normal renal function in whom the risk of neutropenia/agranulocytosis is relatively low (1 out of over 8,600 in clinical trials). Use special precautions in patients with impaired renal function, collagen vascular disorders, or those exposed to other drugs known to affect the white cells or immune response. Evaluation of hypertensives should always include assessment of renal function. Overall, the most frequently occurring adverse reactions associated with CAPOTEN are skin rash and taste alteration; both effects are generally mild, reversible, or self-limited. See INDICATIONS AND USAGE, WARNINGS, and ADVERSE REACTIONS in the brief summary on the adjacent page.

†Based upon the Sexual Symptoms Distress Index.

1. Croog SH, Levine S, Testa MA, et al: The effects of antihypertensive therapy on the quality of life. N Engl J Med 314(26):1657-1664, 1986.

SQUIBB

Means Sharing Love

Staying close can be important to your hypertensive patients. Unfortunately, this aspect of patients' lives can be complicated by drug-induced effects upon sexual function.

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INDICATIONS: Hypertension – CAPOTEN (captopril) is indicated for the treatment of hypertension. Consideration should be given to the risk of neutropenia/agranulocytosis (see WARNINGS). CAPOTEN may be used as initial therapy for patients with normal renal function, in whom the risk is relatively low. In patients with impaired renal function, particularly those with collagen vascular disease, captopril should be reserved for those who have either developed unacceptable side effects on other drugs, or have failed to respond satisfactorily to drug combinations. CAPOTEN is effective alone and in combination with other antihypertensive agents, especially thiazide-type diuretics.

Heart Failure: CAPOTEN (captopril) is indicated in patients with heart failure who have not responded adequately to or cannot be controlled by conventional diuretic and digitalis therapy. CAPOTEN is to be used with diuretics and digitalis.

CONTRAINDICATIONS: CAPOTEN is contraindicated in patients who are hypersensitive to this product.

WARNINGS: Neutropenia/Agranulocytosis – Neutropenia (< 1000/mm³) with myeloid hypoplasia has resulted from use of captopril. About half of the neutropenic patients developed systemic or oral cavity infections or other features of the syndrome of agranulocytosis. The risk of neutropenia is dependent on the clinical status of the patient:

In clinical trials in patients with hypertension who have normal renal function (serum creatinine less than 1.6 mg/dL and no collagen vascular disease), neutropenia has been seen in one patient out of over 8,600 exposed. In patients with some degree of renal failure (serum creatinine at least 1.6 mg/dL) but no collagen vascular disease, the risk in clinical trials was about 1 per 500. Doses were relatively high in these patients, particularly in view of their diminished renal function. In patients with collagen vascular diseases (e.g., systemic lupus erythematosus, scleroderma) and impaired renal function, neutropenia occurred in 3.7% of patients in clinical trials. While none of the over 750 patients in formal clinical trials of heart failure developed neutropenia, it has occurred during the subsequent clinical experience. Of reported cases, about half had serum creatinine ≥1.6 mg/dL and more than 75% received procainamide. In heart failure, it appears that the same risk factors for neutropenia are present.

Neutropenia has appeared usually within 3 months after starting therapy, associated with myeloid hypoplasia and frequently accompanied by erythroid hypoplasia and decreased numbers of megakaryocytes (e.g., hypoplastic bone marrow and pancytopenia); anemia and thrombocytopenia were sometimes seen. Neutrophils generally returned to normal in about 2 weeks after captopril was discontinued, and serious infections were limited to clinically complex patients. About 13% of the cases of neutropenia have ended fatally, but almost all fatalities were in patients with serious illness, having collagen vascular disease, renal failure, heart failure or immunosuppressant therapy, or a combination of these complicating factors. **Evaluation of the hypertensive or heart failure patient should always include assessment of renal function.** If captopril is used in patients with impaired renal function, white blood cell and differential counts should be evaluated prior to starting treatment and at approximately 2-week intervals for about 3 months, then periodically. In patients with collagen vascular disease or who are exposed to other drugs known to affect the white cells or immune response, particularly when there is impaired renal function, captopril should be used only after an assessment of benefit and risk, and then with caution. All patients treated with captopril should be told to report any signs of infection (e.g., sore throat, fever). If infection is suspected, perform white cell counts without delay. Since discontinuation of captopril and other drugs has generally led to prompt return of the white count to normal, upon confirmation of neutropenia (neutrophil count < 1000/mm³) withdraw captopril and closely follow the patient's course.

Proteinuria: Total urinary proteins > 1 g per day were seen in about 0.7% of patients on captopril. About 90% of affected patients had evidence of prior renal disease or received high doses (>150 mg/day), or both. The nephrotic syndrome occurred in about one-fifth of proteinuric patients. In most cases, proteinuria subsided or cleared within 6 months whether or not captopril was continued. The BUN and creatinine were seldom altered in proteinuric patients. Since most cases of proteinuria occurred by the 8th month of therapy with captopril, patients with prior renal disease or those receiving captopril at doses >150 mg per day, should have urinary protein estimates (dip-stick on 1st morning urine) before therapy, and periodically thereafter.

Hypotension: Excessive hypotension was rarely seen in hypertensive patients but is a possibility in severely salt/volume-depleted persons such as those treated vigorously with diuretics (see PRECAUTIONS [Drug Interactions]). In heart failure, where the blood pressure was either normal or low, transient decreases in mean blood pressure >20% were recorded in about half of the patients. This transient hypotension may occur after any of the first several doses and is usually well tolerated, although rarely it has been associated with arrhythmia or conduction defects. A starting dose of 6.25 or 12.5 mg tid may minimize the hypotensive effect. Patients should be followed closely for the first 2 weeks of treatment and whenever the dose of captopril and/or diuretic is increased.

BECAUSE OF THE POTENTIAL FALL IN BLOOD PRESSURE IN THESE PATIENTS, THERAPY SHOULD BE STARTED UNDER VERY CLOSE MEDICAL SUPERVISION.

PRECAUTIONS: General: *Impaired Renal Function* – Hypertension – Some hypertensive patients with renal disease, particularly those with severe renal artery stenosis, have developed increases in BUN and serum creatinine. It may be necessary to reduce captopril dosage and/or discontinue diuretic. For some of these patients, normalization of blood pressure and maintenance of adequate renal perfusion may not be possible. Heart Failure – About 20% of patients develop stable elevations of BUN and serum creatinine >20% above normal or baseline upon long-term treatment. Less than 5% of patients, generally with severe preexisting renal disease, required discontinuation due to progressively increasing creatinine. See DOSAGE AND ADMINISTRATION, ADVERSE REACTIONS [Altered Laboratory Findings]. *Valvular Stenosis* – A theoretical concern, for risk of decreased coronary perfusion, has been noted regarding vasodilator treatment in patients with aortic stenosis due to decreased afterload reduction. *Surgery/Anesthesia* – If hypotension occurs during surgery or anesthesia, and is considered due to the effects of captopril, it is correctable by volume expansion.

Drug Interactions: *Hypotension – Patients on Diuretic Therapy* – Precipitous reduction of blood pressure may occasionally occur within the 1st hour after administration of the initial of captopril dose in patients on diuretics, especially those recently placed on diuretics, and those on severe dietary salt restriction or dialysis. This possibility can be minimized by either discontinuing the diuretic or increasing the salt intake about 1 week prior to initiation of captopril therapy or by initiating therapy with small doses (6.25 or 12.5 mg). Alternatively, provide medical supervision for at least 1 hour after the initial dose.

Agents Having Vasodilator Activity – In heart failure patients, vasodilators should be administered with caution.

Agents Causing Renin Release – Captopril's effect will be augmented by antihypertensive agents that cause renin release.

Agents Affecting Sympathetic Activity – The sympathetic nervous system may be especially important in supporting blood pressure in patients receiving captopril alone or with diuretics. Beta-adrenergic blocking drugs add some further antihypertensive effect to captopril, but the overall response is less than additive. Therefore, use agents affecting sympathetic activity (e.g., ganglionic blocking agents or adrenergic neuron blocking agents) with caution.

Agents Increasing Serum Potassium – Give potassium-sparing diuretics or potassium supplements only for documented hypokalemia, and then with caution, since they may lead to a significant increase of serum potassium. Use potassium-containing salt substitutes with caution.

Inhibitors of Endogenous Prostaglandin Synthesis – Indomethacin and other nonsteroidal anti-inflammatory agents may reduce the antihypertensive effect of captopril, especially in low renin hypertension.

Drug/Laboratory Test Interaction: Captopril may cause a false-positive urine test for acetone.

Carcinogenesis, Mutagenesis and Impairment of Fertility: Two-year studies with doses of 50 to 1350 mg/kg/day in mice and rats failed to show any evidence of carcinogenic potential. Studies in rats have revealed no impairment of fertility.

Pregnancy: Category C: There are no adequate and well-controlled studies in pregnant women. Embryocidal effects and craniofacial malformations were observed in rabbits. Therefore, captopril should be used during pregnancy, or for patients likely to become pregnant, only if the potential benefit outweighs the potential risk to the fetus. Captopril crosses the human placenta.

Nursing Mothers: Captopril is secreted in human milk. Exercise caution when administering captopril to a nursing woman, and, in general, nursing should be interrupted.

Pediatric Use: Safety and effectiveness in children have not been established although there is limited experience with use of captopril in children from 2 months to 15 years of age. Dosage, on a weight basis, was comparable to that used in adults. CAPOTEN (captopril) should be used in children only if other measures for controlling blood pressure have not been effective.

ADVERSE REACTIONS: Reported incidences are based on clinical trials involving approximately 7000 patients.

Renal – About 1 of 100 patients developed proteinuria (see WARNINGS). Renal insufficiency, renal failure, polyuria, oliguria, and urinary frequency in 1 to 2 of 1000 patients.

Hematologic – Neutropenia/agranulocytosis has occurred (see WARNINGS). Anemia, thrombocytopenia, and pancytopenia have been reported.

Dermatologic – Rash, (usually maculopapular, rarely urticarial), often with pruritus, and sometimes with fever and eosinophilia, in about 4 to 7 of 100 patients (depending on renal status and dose), usually during the 1st 4 weeks of therapy. Pruritus, without rash, in about 2 of 100 patients. A reversible associated pemphigoid-like lesion, and photosensitivity, have also been reported. Angioedema of the face, mucous membranes of the mouth, or of the extremities in about 1 of 1000 patients – reversible on discontinuance of captopril therapy. One case of laryngeal edema has been reported. Flushing or pallor in 2 to 5 of 1000 patients.

Cardiovascular – Hypotension may occur; see WARNINGS and PRECAUTIONS [Drug Interactions] for discussion of hypotension on initiation of captopril therapy. Tachycardia, chest pain, and palpitations each in about 1 of 100 patients. Angina pectoris, myocardial infarction, Raynaud's syndrome, and congestive heart failure each in 2 to 3 of 1000 patients.

Dysgeusia – Approximately 2 to 4 (depending on renal status and dose) of 100 patients developed a diminution or loss of taste perception; taste impairment is reversible and usually self-limited even with continued drug use (2 to 3 months). Gastric irritation, abdominal pain, nausea, vomiting, diarrhea, anorexia, constipation, aphthous ulcers, peptic ulcer, dizziness, headache, malaise, fatigue, insomnia, dry mouth, dyspnea, cough, alopecia, paresthesias reported in about 0.5 to 2% of patients but did not appear at increased frequency compared to placebo or other treatments used in controlled trials.

Altered Laboratory Findings: Elevations of liver enzymes in a few patients although no causal relationship has been established. Rarely cholestatic jaundice, and hepatocellular injury with or without secondary cholestasis, have been reported. A transient elevation of BUN and serum creatinine may occur, especially in volume-depleted or renovascular hypertension patients. In instances of rapid reduction of longstanding or severely elevated blood pressure, the glomerular filtration rate may decrease transiently, also resulting in transient rises in serum creatinine and BUN. Small increases in serum potassium concentration frequently occur, especially in patients with renal impairment (see PRECAUTIONS).

OVERDOSAGE: Primary concern is correction of hypotension. Volume expansion with an I.V. infusion of normal saline is the treatment of choice for restoration of blood pressure. Captopril may be removed from the general circulation by hemodialysis.

DOSAGE AND ADMINISTRATION: CAPOTEN (captopril) should be taken one hour before meals. In hypertension, CAPOTEN may be dosed bid or tid. Dosage must be individualized; see DOSAGE AND ADMINISTRATION section of package insert for detailed information regarding dosage in hypertension and in heart failure. Because CAPOTEN (captopril) is excreted primarily by the kidneys, dosage adjustments are recommended for patients with impaired renal function.

Consult package insert before prescribing CAPOTEN (captopril).

HOW SUPPLIED: Available in tablets of 12.5, 25, 50, and 100 mg in bottles of 100 (25 mg and 50 mg also available in bottles of 1000), and in UNIMATIC® unit-dose packs of 100 tablets. (J3-658J)

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†Pooled mean serum potassium following oral administration of 30 mEq K-Tab compared to 24 mEq Slow-K in diuretic-treated hypertensives (n = 20) over 8 weeks.

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References: 1. Data on file, CIBA Pharmaceutical Company 2. Skoutakis VA, Acchiardo SR, Wojciechowski NJ, et al: Liquid and solid potassium chloride Bioavailability and safety. *Pharmacotherapy* 1980;4(6):392-397. 3. Skoutakis VA, Carter CA, Acchiardo SR: Therapeutic assessment of Slow-K and K-Tab potassium chloride formulations in hypertensive patients treated with thiazide diuretics. *Drug Intell Clin Pharm* 1987;21 436-440.

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BRIEF SUMMARY (FOR FULL PRESCRIBING INFORMATION SEE PACKAGE INSERT)

INDICATIONS AND USAGE

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1. For therapeutic use in patients with hypokalemia with or without metabolic alkalosis; in digitalis intoxication and in patients with hypokalemic familial periodic paralysis
2. For prevention of potassium depletion when the dietary intake of potassium is inadequate in the following conditions: patients receiving digitalis and diuretics for congestive heart failure; hepatic cirrhosis with ascites; states of aldosterone excess with normal renal function; potassium-losing nephropathy; and certain diarrheal states
3. The use of potassium salts in patients receiving diuretics for uncomplicated essential hypertension is often unnecessary when such patients have a normal dietary pattern. Serum potassium should be checked periodically, however, and if hypokalemia occurs, dietary supplementation with potassium-containing foods may be adequate to control milder cases. In more severe cases supplementation with potassium salts may be indicated

CONTRAINDICATIONS

Potassium supplements are contraindicated in patients with hyperkalemia, since a further increase in serum potassium concentration in such patients can produce cardiac arrest. Hyperkalemia may complicate any of the following conditions: chronic renal failure, systemic acidosis such as diabetic acidosis, acute dehydration, extensive tissue breakdown as in severe burns, adrenal insufficiency, or the administration of a potassium-sparing diuretic (e.g., spironolactone, triamterene) (see DVERDOSAGE).

All solid dosage forms of potassium supplements are contraindicated in any patient in whom there is cause for arrest or delay in tablet passage through the gastrointestinal tract. In these instances, potassium supplementation should be with a liquid preparation. Wax-matrix potassium chloride preparations have produced esophageal ulceration in certain cardiac patients with esophageal compression due to an enlarged left atrium.

WARNINGS

Hyperkalemia (See DVERDOSAGE).

In patients with impaired mechanisms for excreting potassium, the administration of potassium salts can produce hyperkalemia and cardiac arrest. This occurs most commonly in patients given potassium by the intravenous route but may also occur in patients given potassium orally. Potentially fatal hyperkalemia can develop rapidly and be asymptomatic.

The use of potassium salts in patients with chronic renal disease, or any other condition which impairs potassium excretion, requires particularly careful monitoring of the serum potassium concentration and appropriate dosage adjustment.

Interaction With Potassium-Sparing Diuretics

Hypokalemia should not be treated by the concomitant administration of potassium salts and a potassium-sparing diuretic (e.g., spironolactone or triamterene), since the simultaneous administration of these agents can produce severe hyperkalemia

Gastrointestinal Lesions

Potassium chloride tablets have produced stenotic and/or ulcerative lesions of the small bowel and deaths. These lesions are caused by a high localized concentration of potassium ion in the region of a rapidly dissolving tablet, which injures the bowel wall and thereby produces obstruction, hemorrhage, or perforation. Slow-K is a wax-matrix tablet formulated to provide a controlled rate of release of potassium chloride and thus to minimize the possibility of a high local concentration of potassium ion near the bowel wall. While the reported frequency of small-bowel lesions is much less with wax-matrix tablets (less than one per 100,000 patient-years) than with enteric-coated potassium chloride tablets (40-50 per 100,000 patient-years) cases associated with wax-matrix tablets have been reported both in foreign countries and in the United States. In addition, perhaps because the wax-matrix preparations are not enteric-coated and release potassium in the stomach, there have been reports of upper gastrointestinal bleeding associated with these products. The total number of gastrointestinal lesions remains approximately one per 100,000 patient-years. Slow-K should be discontinued immediately and the possibility of bowel obstruction or perforation considered if severe vomiting, abdominal pain, distention, or gastrointestinal bleeding occurs.

Metabolic Acidosis

Hypokalemia in patients with metabolic acidosis should be treated with an alkalinizing potassium salt such as potassium bicarbonate, potassium citrate, or potassium acetate

PRECAUTIONS

General:

The diagnosis of potassium depletion is ordinarily made by demonstrating hypokalemia in a patient with a clinical history suggesting some cause for potassium depletion. In interpreting the serum potassium level, the physician should bear in mind that acute alkalosis *per se* can produce hypokalemia in the absence of a deficit in total body potassium, while acute acidosis *per se* can increase the serum potassium concentration into the normal range even in the presence of a reduced total body potassium

Information for Patients

Physicians should consider reminding the patient of the following:

To take each dose without crushing, chewing, or sucking the tablets.

To take this medicine only as directed. This is especially important if the patient is also taking both diuretics and digitalis preparations.

To check with the physician if there is trouble swallowing tablets or if the tablets seem to stick in the throat.

To check with the doctor at once if tarry stools or other evidence of gastrointestinal bleeding is noticed

Laboratory Tests

Regular serum potassium determinations are recommended. In addition, during the treatment of potassium depletion, careful attention should be paid to acid-base balance, other serum electrolyte levels, the electrocardiogram, and the clinical status of the patient, particularly in the presence of cardiac disease, renal disease, or acidosis

Drug Interactions

Potassium-sparing diuretics: see WARNINGS

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term carcinogenicity studies in animals have not been performed.

Pregnancy Category C

Animal reproduction studies have not been conducted with Slow-K. It is also not known whether Slow-K can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Slow-K should be given to a pregnant woman only if clearly needed.

Nursing Mothers

The normal potassium ion content of human milk is about 13 mEq/L. It is not known if Slow-K has an effect on this content. Caution should be exercised when Slow-K is administered to a nursing woman.

Pediatric Use

Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

One of the most severe adverse effects is hyperkalemia (see CONTRAINDICATIONS, WARNINGS, and OVERDOSAGE). There also have been reports of upper and lower gastrointestinal conditions including obstruction, bleeding, ulceration, and perforation (see CONTRAINDICATIONS and WARNINGS); other factors known to be associated with such conditions were present in many of these patients.

The most common adverse reactions to oral potassium salts are nausea, vomiting, abdominal discomfort, and diarrhea. These symptoms are due to irritation of the gastrointestinal tract and are best managed by taking the dose with meals or reducing the dose.

Skin rash has been reported rarely.

OVERDOSAGE

The administration of oral potassium salts to persons with normal excretory mechanisms for potassium rarely causes serious hyperkalemia. However, if excretory mechanisms are impaired or if potassium is administered too rapidly intravenously, potentially fatal hyperkalemia can result (see CONTRAINDICATIONS and WARNINGS). It is important to recognize that hyperkalemia is usually asymptomatic and may be manifested only by an increased serum potassium concentration (6.5-8.0 mEq/L) and characteristic electrocardiographic changes (peaking of T waves, loss of P wave, depression of S-T segment, and prolongation of the Q-T interval). Late manifestations include muscle paralysis and cardiovascular collapse from cardiac arrest (9-12 mEq/L).

Treatment measures for hyperkalemia include the following: (1) elimination of foods and medications containing potassium and of potassium-sparing diuretics; (2) intravenous administration of 300-500 ml/hr of 10% dextrose solution containing 10-20 units of insulin per 1,000 ml; (3) correction of acidosis, if present, with intravenous sodium bicarbonate; (4) use of exchange resins, hemodialysis, or peritoneal dialysis.

In treating hyperkalemia in patients who have been stabilized on digitalis, too rapid a lowering of the serum potassium concentration can produce digitalis toxicity

DOSAGE AND ADMINISTRATION

The usual dietary intake of potassium by the average adult is 40-80 mEq per day. Potassium depletion sufficient to cause hypokalemia usually requires the loss of 200 or more mEq of potassium from the total body store. Dosage must be adjusted to the individual needs of each patient but is typically in the range of 20 mEq per day for the prevention of hypokalemia to 40-100 mEq or more per day for the treatment of potassium depletion. Large numbers of tablets should be given in divided doses.

Note: Slow-K slow-release tablets must be swallowed whole and never crushed, chewed, or sucked

HOW SUPPLIED

Tablets—600 mg of potassium chloride (equivalent to 8 mEq) round, buff colored, sugar-coated (imprinted Slow-K)

8 bottles of 100	NDC 0083-0165-30
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Glaxo

IN HYPERTENSION

resistance in the elderly[1]

- ☐ Effective blood pressure control
- ☐ Low incidence of fatigue,[2,3] impotence[2,3] and cold extremities[2-4]

Contraindicated in bronchial asthma, overt cardiac failure, greater-than-first-degree heart block, cardiogenic shock, and severe bradycardia.

See next page for references and Brief Summary of Product Information, which includes a listing of reported adverse reactions.

TRANDATE® *b.i.d.*

labetalol HCl/Glaxo *100 mg/200 mg tablets*

Because it also vasodilates

References: 1. Holtzman JL, Finley O, Johnson B, et al. The effects of single-dose atenolol, labetalol, and propranolol on cardiac and vascular function. *Clin Pharmacol Ther* 1986;40:268-273. 2. Oue OL, Giguere GC, Plachetka JR. Postmarketing comparison of labetalol and propranolol in hypertensive patients. *Clin Ther* 1986;8(6):624-631. 3. Burris JF, Goldstein J, Zager PG, et al. Comparative tolerability of labetalol versus propranolol, atenolol, pindolol, metoprolol, and nadolol. *J Clin Hypertens* 1986;3:1-9. 4. Erb RJ, Plachetka JR. Thermographic evaluation of the peripheral vascular effects of labetalol and propranolol. *Curr Ther Res* 1985;28(1):68-73.

TRANDATE® Tablets
(labetalol hydrochloride)

BRIEF SUMMARY OF PRODUCT INFORMATION

The following is a brief summary only. Before prescribing, see complete prescribing information in TRANDATE® Tablets product labeling.

INDICATIONS AND USAGE: TRANDATE® Tablets are indicated in the management of hypertension. TRANDATE Tablets may be used alone or in combination with other antihypertensive agents, especially thiazide and loop diuretics.

CONTRAINDICATIONS: TRANDATE® Tablets are contraindicated in bronchial asthma, overt cardiac failure, greater-than-first-degree heart block, cardiogenic shock, and severe bradycardia (see **WARNINGS**).

WARNINGS: Cardiac Failure: Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure. Beta-blockade carries a potential hazard of further depressing myocardial contractility and precipitating more severe failure. Although beta-blockers should be avoided in overt congestive heart failure, if necessary labetalol HCl can be used with caution in patients with a history of heart failure who are well compensated. Congestive heart failure has been observed in patients receiving labetalol HCl. Labetalol HCl does not abolish the inotropic action of digitalis on heart muscle.

In Patients Without a History of Cardiac Failure: In patients with latent cardiac insufficiency, continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or be given a diuretic, and the response should be observed closely. If cardiac failure continues despite adequate digitalization and diuretic, TRANDATE® therapy should be withdrawn (gradually, if possible).

Exacerbation of Ischemic Heart Disease Following Abrupt Withdrawal: Angina pectoris has not been reported upon labetalol HCl discontinuation. However, hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy; exacerbation of angina and, in some cases, myocardial infarction have occurred after *abrupt* discontinuation of such therapy. When discontinuing chronically administered TRANDATE, particularly in patients with ischemic heart disease, the dosage should be gradually reduced over a period of one to two weeks and the patient should be carefully monitored. If angina markedly worsens or acute coronary insufficiency develops, TRANDATE administration should be reinstituted promptly, at least temporarily, and other measures appropriate for the management of unstable angina should be taken. Patients should be warned against interruption or discontinuation of therapy without the physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue TRANDATE therapy abruptly even in patients treated only for hypertension.

Nonallergic Bronchospasm (eg, Chronic Bronchitis and Emphysema): Patients with bronchospastic disease should, in general, not receive beta-blockers. TRANDATE may be used with caution, however, in patients who do not respond to, or cannot tolerate, other antihypertensive agents. It is prudent, if TRANDATE is used, to use the smallest effective dose, so that inhibition of endogenous or exogenous beta-agonists is minimized.

Pheochromocytoma: Labetalol HCl has been shown to be effective in lowering blood pressure and relieving symptoms in patients with pheochromocytoma. However, paradoxical hypertensive responses have been reported in a few patients with this tumor; therefore, use caution when administering labetalol HCl to patients with pheochromocytoma.

Diabetes Mellitus and Hypoglycemia: Beta-adrenergic blockade may prevent the appearance of premonitory signs and symptoms (eg, tachycardia) of acute hypoglycemia. This is especially important with labile diabetics. Beta-blockade also reduces the release of insulin in response to hyperglycemia; it may therefore be necessary to adjust the dose of antidiabetic drugs.

Major Surgery: The necessity or desirability of withdrawing beta-blocking therapy prior to major surgery is controversial. Protracted severe hypotension and difficulty in restarting or maintaining a heartbeat have been reported with beta-blockers. The effect of labetalol HCl's alpha-adrenergic activity has not been evaluated in this setting.

A synergism between labetalol HCl and halothane anesthesia has been shown (see **Drug Interactions** under **PRECAUTIONS**).

PRECAUTIONS: General: *Impaired Hepatic Function:* TRANDATE® Tablets should be used with caution in patients with impaired hepatic function since metabolism of the drug may be diminished.

Jaundice or Hepatic Dysfunction: On rare occasions, labetalol HCl has been associated with jaundice (both hepatic and cholestatic). It is therefore recommended that treatment with labetalol HCl be stopped immediately should a patient develop jaundice or laboratory evidence of liver injury. Both have been shown to be reversible on stopping therapy.

Information for Patients: As with all drugs with beta-blocking activity, certain advice to patients being treated with labetalol HCl is warranted. This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects. While no incidence of the abrupt withdrawal phenomenon (exacerbation of angina pectoris) has been reported with labetalol HCl, dosing with TRANDATE Tablets should not be interrupted or discontinued without a physician's advice. Patients being treated with TRANDATE Tablets should consult a physician at any sign of impending cardiac failure. Also, transient scalp tingling may occur, usually when treatment with TRANDATE Tablets is initiated (see **ADVERSE REACTIONS**).

Laboratory Tests: As with any new drug given over prolonged periods, laboratory parameters should be observed over regular intervals. In patients with concomitant illnesses, such as impaired renal function, appropriate tests should be done to monitor these conditions.

Drug Interactions: In one survey, 2.3% of patients taking labetalol HCl in combination with tricyclic antidepressants experienced tremor as compared to 0.7% reported to occur with labetalol HCl alone. The contribution of each of the treatments to this adverse reaction is unknown, but the possibility of a drug interaction cannot be excluded.

Drugs possessing beta-blocking properties can blunt the bronchodilator effect of beta-receptor agonist drugs in patients with bronchospasm; therefore, doses greater than the normal antiasthmatic dose of beta-agonist bronchodilator drugs may be required.

Cimetidine has been shown to increase the bioavailability of labetalol HCl. Since this could be explained either by enhanced absorption or by an alteration of hepatic metabolism of labetalol HCl, special care should be used in establishing the dose required for blood pressure control in such patients.

Synergism has been shown between halothane anesthesia and intravenously administered labetalol HCl. During controlled hypotensive anesthesia using labetalol HCl in association with halothane, high concentrations (3% or above) of halothane should not be used because the degree of hypotension will be increased and because of the possibility of a large reduction in cardiac output and an increase in central venous pressure. The anesthesiologist should be informed when a patient is receiving labetalol HCl.

Labetalol HCl blunts the reflex tachycardia produced by nitroglycerin without preventing its hypotensive effect. If labetalol HCl is used with nitroglycerin in patients with angina pectoris, additional antihypertensive effects may occur.

Drug/Laboratory Test Interactions: The presence of a metabolite of labetalol in the urine may result in falsely increased levels of urinary catecholamines when measured by a nonspecific trihydroxyindole (THI) reaction. In screening patients suspected of having a pheochromocytoma and being treated with labetalol HCl, specific radioenzymatic or high performance liquid chromatography assay techniques should be used to determine levels of catecholamines or their metabolites.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term oral dosing studies with labetalol HCl for 18 months in mice and for two years in rats showed no evidence of carcinogenesis. Studies with labetalol HCl using dominant lethal assays in rats and mice and exposing microorganisms according to modified Ames tests showed no evidence of mutagenesis.

Pregnancy: ***Teratogenic Effects: Pregnancy Category C:*** Teratogenic studies have been performed with labetalol in rats and rabbits at oral doses up to approximately six and four times the maximum recommended human dose (MRHD), respectively. No reproducible evidence of fetal malformations was observed. Increased fetal resorptions were seen in both species at doses approximating the MRHD. There are no adequate and well-controlled studies in pregnant women. Labetalol should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects: Infants of mothers who were treated with labetalol HCl during pregnancy did not appear to be adversely affected by the drug. Oral administration of labetalol to rats during late gestation through weaning at doses of two to four times the MRHD caused a decrease in neonatal survival.

Labor and Delivery: Labetalol HCl given to pregnant women with hypertension did not appear to affect the usual course of labor and delivery.

Nursing Mothers: Small amounts of labetalol (approximately 0.004% of the maternal dose) are excreted in human milk. Caution should be exercised when TRANDATE Tablets are administered to a nursing woman.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: Most adverse effects are mild, transient, and occur early in the course of treatment. In controlled clinical trials of three to four months' duration, discontinuation of TRANDATE® Tablets due to one or more adverse effects was required in 7% of all patients. In these same trials, beta-blocker control agents led to discontinuation in 8% to 10% of patients, and a centrally acting alpha-agonist in 30% of patients.

The following adverse reactions were derived from multi-center, controlled clinical trials over treatment periods of three and four months. The rates, which ranged from less than 1% to 5% except as otherwise noted, are based on adverse reactions considered probably drug-related by the investigator. If all reports are considered, the rates are somewhat higher (eg, dizziness, 20%; nausea, 14%; fatigue, 11%).

Body as a Whole: Fatigue, asthenia, and headache.

Gastrointestinal: Nausea (6%), vomiting, dyspepsia, diarrhea, and taste distortion.

Central and Peripheral Nervous Systems: Dizziness (11%), paresthesia, and drowsiness.

Autonomic Nervous System: Nasal stuffiness, ejaculation failure, impotence, and increased sweating.

Cardiovascular: Edema and postural hypotension.

Respiratory: Dyspnea.

Skin: Rash.

Special Senses: Vision abnormality and vertigo.

The adverse effects were reported spontaneously and are representative of the incidence of adverse effects that may be observed in a properly selected hypertensive patient population, ie, a group excluding patients with bronchospastic disease, overt congestive heart failure, or other contraindications to beta-blocker therapy.

Clinical trials also included studies utilizing daily doses up to 2,400 mg in more severely hypertensive patients. The US therapeutic trials data base for adverse reactions that are clearly or possibly dose-related shows that the following side effects increased with increasing dose: dizziness, fatigue, nausea, vomiting, dyspepsia, paresthesia, nasal stuffiness, ejaculation failure, impotence, and edema.

In addition, a number of other less common adverse events have been reported in clinical trials or the literature:

Cardiovascular: Postural hypotension, including rarely, syncope.

Central and Peripheral Nervous Systems: Paresthesias, most frequently described as scalp tingling. In most cases, it was mild, transient, and usually occurred at the beginning of treatment.

Collagen Disorders: Systemic lupus erythematosus; positive antinuclear factor (ANF).

Eyes: Dry eyes.

Immunological System: Antimitochondrial antibodies.

Liver and Biliary System: Cholestasis with or without jaundice.

Musculoskeletal System: Muscle cramps; toxic myopathy.

Respiratory System: Bronchospasm.

Skin and Appendages: Rashes of various types, such as generalized maculopapular, lichenoid, urticarial, bullous lichen planus, psoriaform, and facial erythema; Peyronie's disease; reversible alopecia.

Urinary System: Difficulty in micturition, including acute urinary bladder retention.

Following approval for marketing in the United Kingdom, a monitored release survey involving approximately 6,800 patients was conducted for further safety and efficacy evaluation of this product. Results of this survey indicate that the type, severity, and incidence of adverse effects were comparable to those cited above.

Potential Adverse Effects: In addition, other adverse effects not listed above have been reported with other beta-adrenergic blocking agents.

Central Nervous System: Reversible mental depression progressing to catatonia, an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance or neuropsychometrics.

Cardiovascular: Intensification of AV block (see **CONTRAINDICATIONS**).

Allergic: Fever combined with aching and sore throat; laryngospasm; respiratory distress.

Hematologic: Agranulocytosis; thrombocytopenic or nonthrombocytopenic purpura.

Gastrointestinal: Mesenteric artery thrombosis; ischemic colitis.

The oculomucocutaneous syndrome associated with the beta-blocker practolol has not been reported with labetalol HCl.

Clinical Laboratory Tests: There have been reversible increases of serum transaminases in 4% of patients treated with labetalol HCl and tested, and more rarely, reversible increases in blood urea.

OVERDOSAGE: Information concerning possible overdosage and its treatment appears in the full prescribing information.

DOSAGE AND ADMINISTRATION: DOSAGE MUST BE INDIVIDUALIZED. The recommended *initial* dosage is 100 mg *twice* daily whether used alone or added to a diuretic regimen. After two or three days, using standing blood pressure as an indicator, dosage may be titrated in increments of 100 mg bid every two or three days. The usual *maintenance* dosage of labetalol HCl is between 200 and 400 mg *twice* daily. Before use, see complete prescribing information for dosage details.

HOW SUPPLIED: TRANDATE® Tablets, 100 mg, light orange, round, scored, film-coated tablets engraved on one side with "TRANDATE 100 GLAXO," bottles of 100 (NDC 0173-0346-43) and 500 (NDC 0173-0346-44) and unit dose packs of 100 tablets (NDC 0173-0346-47).

TRANDATE Tablets, 200 mg, white, round, scored, film-coated tablets engraved on one side with "TRANDATE 200 GLAXO," bottles of 100 (NDC 0173-0347-43) and 500 (NDC 0173-0347-44) and unit dose packs of 100 tablets (NDC 0173-0347-47).

TRANDATE Tablets, 300 mg, peach, round, scored, film-coated tablets engraved on one side with "TRANDATE 300 GLAXO," bottles of 100 (NDC 0173-0348-43) and 500 (NDC 0173-0348-44) and unit dose packs of 100 tablets (NDC 0173-0348-47).

TRANDATE Tablets should be stored between 2° and 30°C (36° and 86°F). TRANDATE Tablets in the unit dose boxes should be protected from excessive moisture.

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September 1986

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The following list of continuing medical education programs in Arizona is compiled by the Arizona Medical Association. All courses listed have been certified as meeting the criteria for Category I of the ArMA CME Certificate and the AMA Physicians Recognition Award. To list Category I continuing medical education programs, please send information to Arizona Medical Association, 810 West Bethany Home Road, Phoenix, AZ 85013; or phone (602) 246-8901.

Brochures and registration forms are available from the contact person or organization sponsoring the program.

March 17-19—**24th Annual Arizona Chest Symposium.** Doubletree Hotel, Tucson. Thurs-Sat. Contact: Susan Thornton, RN, MS, Tucson Medical Center, (602) 327-5461, Ext. 5110.

March 22-25—**Pediatric Update 1988.** La Posada Resort Hotel, Scottsdale. Tues-Fri. Contact: Paul C. Stillwell, MD, Phoenix Children's Hospital, (602) 239-5778.

March 23-27—**12th Annual Valley of the Sun Dermatologic Symposium.** Stouffers Cottonwoods Resort, Scottsdale. Wed-Sun. Contact: Phoenix Dermatologic Society, c/o Susan Slama, MD, (602) 991-3203.

April 30—**Medical and Psychological Perspectives of Post-Polio Sequelae.** Ramada Inn Airport North, Phoenix. Sat. Contact: Pat Caldwell, Arizona Easter Seal Society, (602) 252-6061.

June 9—**Arizona Medical Association Annual Scientific Session.** Loews Ventana Canyon Resort, Tucson. Thurs. Contact: ArMA.

PATHOLOGY

May 14-15—**Selected Topics in Gynecologic Pathology.** Arizona Society of Pathologists and U of A at Westward Look Resort, Tucson. Sat-Sun. 7 hrs. Contact: Beverly Richter, Arizona Society of Pathologists, 810 W Bethany Home Rd, Phoenix 85013. (602) 246-8901.

CONTACT INFORMATION

ArMA—Contact: Arizona Medical Association, 810 W Bethany Home Rd, Phoenix, AZ 85013. (602) 246-8901.

U of A—Contact: University of Arizona College of Medicine, Arizona Health Sciences Center, Tucson, AZ 85724. (602) 626-6707.

CALIFORNIA, HAWAII AND NEVADA

This listing of continuing education programs in California, Hawaii and Nevada is supplied by the Committee on Continuing Medical Education of the California Medical Association. All courses and meetings listed have been approved for Category I credit toward the CMA Certificate in Continuing Medical Education. To have accredited courses listed here, please send information at least two months in advance to Department of Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690; or phone (415) 863-5522. For a list of organizations approved for Category I credit toward the CMA Certificate in Continuing Medical Education or for more information on accreditation or certification, please write to the above address.

ALLERGY

March 28-30—**Office and Hospital Based Clinical Nutrition for the Practitioner.** University of Washington at Maui, Hawaii. Mon-Wed. Contact: U/W School of Medicine, Div of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

ANESTHESIOLOGY

March 19-20—**33rd Postgraduate Assembly.** Los Angeles Society of Anesthesiologists at Los Angeles Hilton Hotel. Sat-Sun. Contact: Laura Lee, Los Angeles Society of Anesthesiologists, PO Box 3465, Los Angeles, 90051-1465. (213) 483-1581 ext. 320.

May 15-20—**Hawaiian Seminar on Clinical Anesthesia.** California Society of Anesthesiologists at Sheraton Kauai Hotel, Poipu Beach, Kauai. Sun-Fri. 20 hrs. $325-375. Contact: California Society of Anesthesiologists, 1065 Hillsdale Blvd, #410, Foster City 94404. (415) 345-3020.

May 16-20—**5th International Symposium: Computing in Anesthesia and Intensive Care.** UCSD at US Grant Hotel, San Diego. Mon-Fri. 20 hrs. $300. Contact: UCSD.

June 16-19—**California Society of Anesthesiologists 1988 Annual Meeting** at Marriott Hotel, Anaheim. Thurs-Sun. 16 hrs. $150-225. Contact: California Society of Anesthesiologists, 1065 Hillsdale Blvd, #410, Foster City 94404. (415) 345-3020.

KEY TO ABBREVIATIONS

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690. (415) 863-5522.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Herbert M. Thomas, MD, MPH, Director of CME, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th Street, Los Angeles 90059. (213) 603-3183.

LLU: Loma Linda University
Contact: Varner J. Johns, Jr, MD, Associate Dean for Continuing Medical Education, Loma Linda University School of Medicine, Loma Linda 92354. (714) 796-7311, ext 2400.

PMC: Pacific Medical Center
Contact: Continuing Education, Pacific Medical Center, PO Box 7999, San Francisco 94120. (415) 563-4321, ext 2761.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Medical School Office Building, Suite X-365, Stanford 94305-6114. (415) 723-5594.

UCD: University of California, Davis
Contact: Ruth Feryok, Director, Office of Continuing Medical Education, University of California, Davis, School of Medicine, 2701 Stockton Boulevard, Sacramento 95817. (916) 453-5390.

UCI: University of California, Irvine
Contact: Melvin I. Marks, MD, Assistant Dean, University of California, Irvine, California College of Medicine, c/o UCI/CME Program, Memorial Medical Center, 2801 Atlantic Avenue, Long Beach 90801-1428. (213) 595-3811, or (714) 856-5414, UCI Extension.

UCLA: University of California, Los Angeles
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, PO Box 24902, UCLA, Los Angeles 90024. (213) 825-7241.

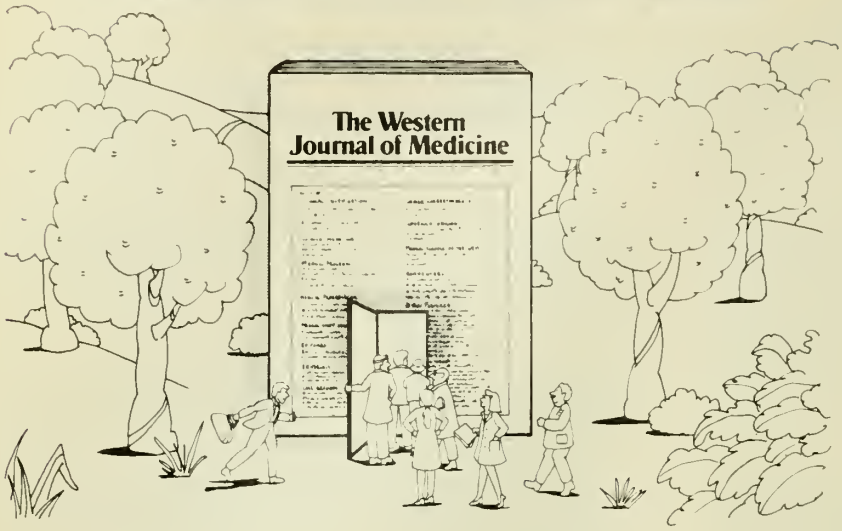
UCSD: University of California, San Diego
Contact: Office of Continuing Medical Education, University of California, San Diego, School of Medicine (M-017), La Jolla 92093. (619) 534-3713.

UCSF: University of California, San Francisco
Contact: Robert Maggio, Administrative Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 476-4251.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 1975 Zonal Ave, KAM314, Los Angeles 90033. (213) 224-7051.

(Continued on Page 294)

Inside Information



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CARAFATE (sucralfate)

BRIEF SUMMARY

CONTRAINDICATIONS
There are no known contraindications to the use of sucralfate.

PRECAUTIONS
Duodenal ulcer is a chronic, recurrent disease. While short-term treatment with sucralfate can result in complete healing of the ulcer, a successful course of treatment with sucralfate should not be expected to alter the post-healing frequency or severity of duodenal ulceration.

Drug Interactions: Animal studies have shown that the simultaneous administration of CARAFATE with tetracycline, phenytoin, or cimetidine will result in a statistically significant reduction in the bioavailability of these agents. This interaction appears to be nonsystemic in origin, presumably resulting from these agents being bound by CARAFATE in the gastrointestinal tract. The bioavailability of these agents may be restored simply by separating the administration of these agents from that of CARAFATE by two hours. The clinical significance of these animal studies is yet to be defined.

Carcinogenesis, Mutagenesis, Impairment of Fertility: No evidence of drug-related tumorigenicity was found in chronic oral toxicity studies of 24 months' duration conducted in mice and rats at doses up to 1 gm/kg (12 times the human dose). A reproduction study in rats at doses up to 38 times the human dose did not reveal any indication of fertility impairment. Mutagenicity studies have not been conducted.

Pregnancy: Pregnancy Category B. Teratogenicity studies have been performed in mice, rats, and rabbits at doses up to 50 times the human dose and have revealed no evidence of harm to the fetus due to sucralfate. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when sucralfate is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS
Adverse reactions to sucralfate in clinical trials were minor and only rarely led to discontinuation of the drug. In studies involving over 2,500 patients, adverse effects were reported in 121 (4.7%). Constipation was the most frequent complaint (2.2%). Other adverse effects, reported in no more than one of every 350 patients, were diarrhea, nausea, gastric discomfort, indigestion, dry mouth, rash, pruritus, back pain, dizziness, sleepiness, and vertigo.

DOSAGE AND ADMINISTRATION
The recommended adult oral dosage for duodenal ulcer is 1 gm four times a day on an empty stomach.

Antacids may be prescribed as needed for relief of pain but should not be taken within one-half hour before or after sucralfate.

While healing with sucralfate may occur during the first week or two, treatment should be continued for 4 to 8 weeks unless healing has been demonstrated by x-ray or endoscopic examination.

HOW SUPPLIED
CARAFATE (sucralfate) 1-gm pink tablets are supplied in bottles of 100 and in Unit Dose Identification Paks of 100. The tablets are embossed with MARION/1712. Issued 3/84

References:
1. Grossman MI: *Scand J Gastroenterol* 58 (suppl 15): 7-16, 1980.
2. Marks IN, in Hellemans J, Vantrappen G (eds): *Gastrointestinal Tract Disorders in the Elderly.* Edinburgh, Churchill Livingstone, 70-81, 1984.
3. Krentz K, Jablonowski H, in Hellemans J, Vantrappen G (eds): *Gastrointestinal Tract Disorders in the Elderly.* Edinburgh, Churchill Livingstone, 62-69, 1984.

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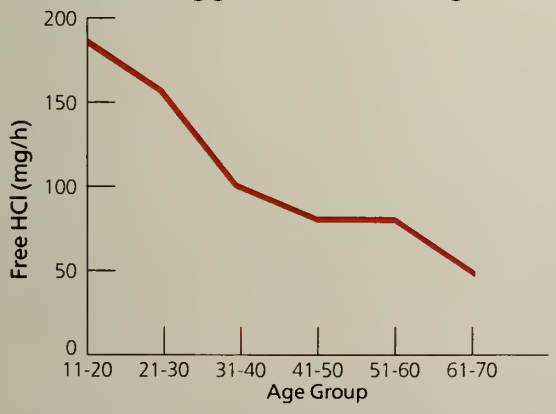
Specialized ulcer therapy

When advancing age signals reduced acid secretion

If your duodenal ulcer patient is over 55, decreased mucosal resistance is more likely to cause an ulcer than hypersecretion of acid-pepsin.[1] A tendency toward lower acid secretion with advancing age has been shown.[2,3]

Declining gastric secretion and age[3]



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Please see adjoining page for references and brief summary of prescribing information.

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The portrait of anxiety

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Please see adjacent page for brief summary of prescribing information.

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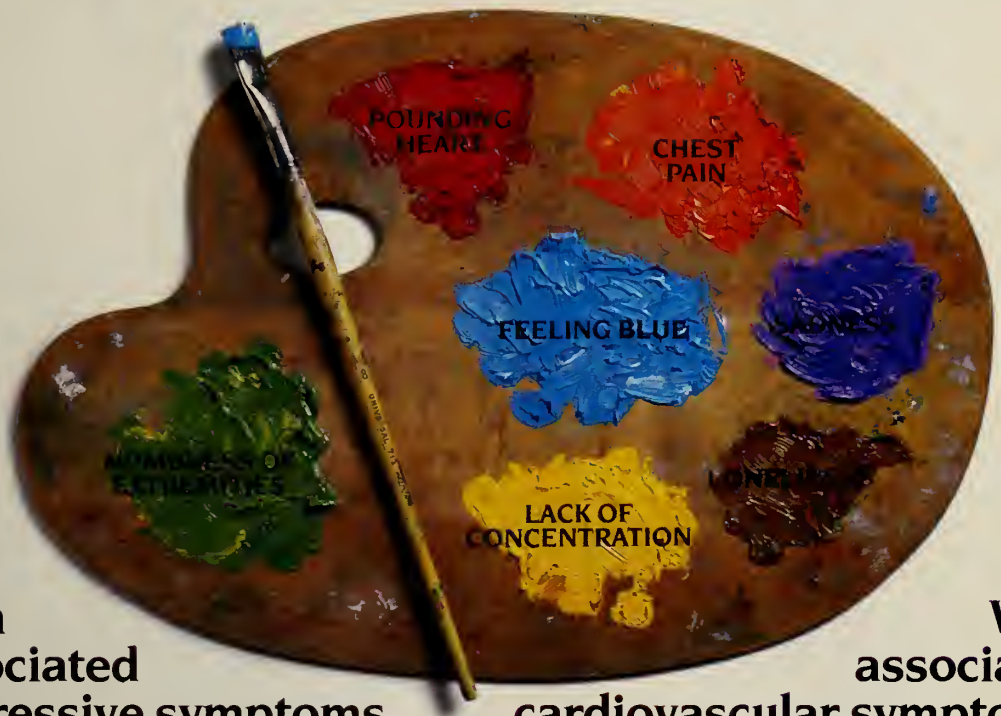
is often complicated



With associated depressive symptoms.

In double-blind, four-week clinical trials in 632 patients with moderate to severe anxiety, therapy with XANAX was compared with placebo.

XANAX was significantly more effective ($P<.001$) than placebo in relieving the anxiety, with over half of the patients showing marked to moderate improvement by the first evaluation period (one week).

In addition, over 70% of these patients experienced associated moderate to severe depressed mood. XANAX was shown to be significantly more effective ($P<.014$) than placebo in improving the associated depressed mood.

With associated cardiovascular symptoms.

Almost 60% of patients in the study had anxiety with associated cardiovascular symptoms even though cardiovascular disease had been ruled out. XANAX was shown to effectively relieve anxiety including the associated cardiovascular symptoms.

XANAX, the first of a unique class—the triazolobenzodiazepines.

- *Well tolerated*—Side effects, if they occur, are generally observed at the beginning of therapy and usually disappear with continued medication. Drowsiness and light-headedness were the most commonly reported adverse reactions.
- *Sustained efficacy*—No reported increase in dosage during 16-week clinical study, once an appropriate dosage was achieved. Since long-term effectiveness of XANAX has not been established, it is recommended that it not be used for longer than 16 weeks.
- *Simple dosage*—0.25 to 0.5 mg t.i.d.

TABLETS 0.25, 0.5 & 1 MG

Xanax®

alprazolam IV

for the relief of complicated anxiety

XANAX® Tablets
(alprazolam) C

CONTRAINDICATIONS
Patients with sensitivity to this drug or other benzodiazepines and in acute narrow angle glaucoma.

WARNINGS
Not of value in psychotic patients. Caution patients against hazardous occupations requiring complete mental alertness and about the simultaneous ingestion of alcohol and other CNS depressant drugs.

Benzodiazepines can cause fetal harm in pregnant women. Warn patients of the potential hazard to the fetus. Avoid during the first trimester.

PRECAUTIONS
General: The dosage of XANAX Tablets should be reduced or withdrawn gradually, since withdrawal seizures have been reported upon abrupt withdrawal. If XANAX is combined with other psychotropics or anticonvulsant drugs, consider drug potentiation (see Drug Interaction section). Exercise the usual precautions regarding size of the prescription for depressed or suicidal patients. In elderly and debilitated patients, use the lowest possible dosage (see Dosage and Administration). Observe the usual precautions in treating patients with impaired renal or hepatic function.

Information for Patients: Alert patients about: (a) consumption of alcohol and drugs, (b) possible fetal abnormalities, (c) operating machinery or driving, (d) not increasing dose of the drug due to risk of dependence, (e) not stopping the drug abruptly. *Laboratory Tests:* Not ordinarily required in otherwise healthy patients. *Drug Interactions:* Additive CNS depressant effects with other psychotropics, anticonvulsants, antihistamines, ethanol and other CNS depressants. Pharmacokinetic interactions with other drugs, e.g., cimetidine, have been reported. *Drug/Laboratory Test Interactions:* No consistent pattern for a drug or test. *Carcinogenesis, Mutagenesis, Impairment of Fertility:* No carcinogenic potential or impairment of fertility in rats. *Pregnancy:* See Warnings. *Nonteratogenic Effects:* The child born of a mother on benzodiazepines may be at some risk for withdrawal symptoms and neonatal flaccidity. *Labor and Delivery:* No established use. *Nursing Mothers:* Benzodiazepines are excreted in human milk. Women on XANAX should not nurse. *Pediatric Use:* Safety and effectiveness in children below the age of 18 have not been established.

ADVERSE REACTIONS
Side effects are generally observed at the beginning of therapy and usually disappear with continued medication. In the usual patient, the most frequent side effects are likely to be an extension of the pharmacologic activity of XANAX, e.g., drowsiness or lightheadedness.

Central nervous system: Drowsiness, lightheadedness, depression, headache, confusion, insomnia, nervousness, syncope, dizziness, akathisia, and tiredness/sleepiness. *Gastrointestinal:* Dry mouth, constipation, diarrhea, nausea/vomiting, and increased salivation. *Cardiovascular:* Tachycardia/palpitations, and hypotension. *Sensory:* Blurred vision. *Musculoskeletal:* Rigidity and tremor. *Cutaneous:* Dermatitis/allergy. *Other side effects:* Nasal congestion, weight gain, and weight loss.

Withdrawal seizures have been reported upon rapid decrease or abrupt discontinuation of XANAX. (See Precautions.)

In addition, the following adverse events have been reported with the use of benzodiazepines: dystonia, irritability, concentration difficulties, anorexia, transient amnesia or memory impairment, loss of coordination, fatigue, sedation, slurred speech, jaundice, musculoskeletal weakness, pruritus, diplopia, dysarthria, changes in libido, menstrual irregularities, incontinence and urinary retention.

Paradoxical reactions such as stimulation, agitation, increased muscle spasticity, sleep disturbances, and hallucinations may occur. Should these occur, discontinue the drug.

During prolonged treatment, periodic blood counts, urinalysis, and blood chemistry analysis are advisable. Minor EEG changes, of unknown significance, have been observed.

DRUG ABUSE AND DEPENDENCE
Physical and Psychological Dependence: Withdrawal symptoms have occurred following abrupt discontinuance of benzodiazepines. Withdrawal seizures have occurred upon rapid decrease or abrupt discontinuation of therapy. In all patients, dosage should be gradually tapered under close supervision. Patients with a history of seizures or epilepsy should not be abruptly withdrawn from XANAX. Addiction-prone individuals should be under careful surveillance. *Controlled Substance Class:* XANAX is a controlled substance and has been assigned to schedule IV.

OVERDOSAGE
Manifestations include somnolence, confusion, impaired coordination, diminished reflexes and coma. No delayed reactions have been reported.

DOSAGE AND ADMINISTRATION
Dosage should be individualized.

The usual starting dose is 0.25 to 0.5 mg, t.i.d. Maximum total daily dose is 4 mg. In the elderly or debilitated, the usual starting dose is 0.25 mg, two or three times daily. Reduce dosage gradually when terminating therapy, by no more than 0.5 milligram every three days.

HOW SUPPLIED
XANAX Tablets are available as 0.25 mg, 0.5 mg, and 1 mg tablets.

Caution: Federal law prohibits dispensing without prescription. B-5-S

Upjohn THE UPJOHN COMPANY 1-7384
Kalamazoo, Michigan 49001 USA February 1987

CONTINUING MEDICAL EDUCATION

(Continued from Page 289)

August 21-27—**Hawaiian Seminar on Clinical Anesthesia.** California Society of Anesthesiologists at Inter-Continental Hotel, Wailea, Maui. Sun-Sat. 20 hrs. $325/$375. Contact: CSA, 1065 E. Hilldale Blvd, Suite 410, Foster City 94404. (415) 345-3020.

October 16-21—**Hawaiian Seminar on Clinical Anesthesia.** California Society of Anesthesiologists at Westin Maui Hotel, Maui. Sun-Fri. 20 hrs. $325/$375. Contact: CSA, 1065 Hilldale Blvd, Suite 410, Foster City 94404. (415) 345-3020.

CARDIOLOGY

March 21-23—**New Directions in Cardiac Rehabilitation.** ACC & Stanford University School of Medicine at Stanford. Mon-Wed. Contact: Registration Secretary EP Dept., ACC, Bethesda, MD (301) 897-5400.

March 23-25—**New Directions in Cardiac Rehabilitation.** Stanford at Stanford University. Wed-Fri. Contact: Stanford.

March 25-27—**Coronary Heart Disease: Current Concepts.** Medical Education Resources at Inter-Continental Hotel, Maui, Hawaii. Fri-Sun. 11-13 hrs. $225-$295. Contact: MER, 5808 S. Rapp St., Suite 202, Littleton, CO 80120. (800) 421-3756.

April 15-17—**Coronary Artery Disease: A Commemorative Symposium—75 Years Since Anitschkow and Herrick.** UCSF. Contact: UCSF.

April 18-27—**Cardiology for the Consultant.** Scripps Clinic and Research Foundation at the Inn at Rancho Santa Fe, Rancho Santa Fe. Mon-Wed. 40 hrs. $900. Contact: Bonny Mower, 10666 N. Torrey Pines Road, La Jolla, 92037. (619) 457-8556.

May 13-14—**Coronary Heart Disease: Current Concepts.** Medical Education Resources at Hilton Hotel, San Francisco. Wed-Thur. 11-13 hrs. $225-$295. Contact: MER, 5808 S. Rapp St., Suite 202, Littleton, CO 80120. (800) 421-3756.

May 19-20—**Cardiology for the Non-Cardiologist.** UCI. Thurs-Fri. Contact: UCI.

June 6-8—**Advanced Echocardiography & Doppler Ultrasound 1988.** American College of Cardiology at Sheraton Harbor Island, San Diego. Mon-Wed. Contact: Registration Secretary, EP Dept. ACC, 9111 Old Georgetown Road, Bethesda, MD 20814.

June 30-July 2—**Consultative Cardiology: Update in Diagnostic and Therapeutic Techniques.** ACC, Orange Coast Heart Institute and Hoag Memorial Hospital at Westin South Coast Plaza, Costa Mesa. Thur-Sat. Contact: Registration Secretary, EP Dept., ACC, 9111 Old Georgetown Road, Bethesda, MD 20814.

DERMATOLOGY

May 21—**Summary of Clinical Use of Argon, YAG, and CO2 Lasers for Cutaneous Lesions.** Palo Alto Medical Foundation at Palo Alto Medical Clinic. Sat. 6 hrs. Contact: Palo Alto Medical Clinic, 300 Homer Ave, Palo Alto 94301. (415) 321-4121.

August 12-14—**Dermatologic Surgery: State of the Art 1988.** Stanford University at Monterey Sheraton, Monterey. Fri-Sun. Contact: Paul H. Jacobs, MD, Dept. of Dermatology, UMC Stanford, 94305. (415) 723-6105.

August 21-28—**International Symposium: Hot Spots in Dermatology.** Kauai Medical Group at Molokai, Hawaii. One week. Contact: David Elpern, MD, 3420-B Kuhio Highway, Lihue, Hawaii 96766. (808) 245-1507.

EMERGENCY MEDICINE

March 23-25—**Advances in Emergency Medicine.** UCSF at Holiday Inn Union Square, San Francisco. Wed-Fri. $300. Contact: UCSF.

March 25-26—**Advances in Emergency Medicine: Toxicology and Infectious Diseases.** UCLA at San Diego Hilton, Mission Bay. Fri-Sat. 9 hrs. Contact: UCLA.

May 11-15—**Tenth Annual Wound Management Workshop.** UCSD at San Diego Hilton Beach and Tennis Resort. Wed-Sun. 19 hrs. Contact: Edith S. Bookstein/WMW, PO Box 1386, La Jolla 92038. (619) 454-3212.

(Continued on Page 362)

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References:

1. Moss SJ: The worldwide decline in caries prevention, in Mead Johnson Clinical Report Series, Clinical Importance of Fluoride Nutrition in Infants, Children, and Young Adults. Chicago, Pragmaton® 1985, Number 1, p. 2.

2. Newbrun E: How fluoride works: Topical vs. systemic action, in Mead Johnson Clinical Report Series, Clinical Importance of Fluoride Nutrition in Infants, Children, and Young Adults. Chicago, Pragmaton® 1985, Number 1, p. 5.

3. Aasenden R and Peebles T: Effects of fluoride supplementation from birth on human deciduous and permanent teeth. *Arch Oral Biol* 1974;19:321.

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NUTRITIONAL DIVISION

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Routine VI-FLOR* supplementation

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INDICATIONS AND USAGE: Prophylaxis of vitamin deficiencies and dental caries in children and adults when fluoride of water supply does not exceed 0.7 ppm.[1,2,3] And, in the case of TRI-VI-FLOR* 0.25 mg Drops with Iron and POLY-VI-FLOR* Drops and Chewable Tablets with Iron, prophylaxis against iron deficiencies. Note: VI-FLOR Drops do not contain folic acid because the vitamin is not stable in liquid form.

PRECAUTIONS: Do not exceed recommended dose or give concurrently with other medications containing significant amounts of fluoride. Prolonged excessive fluoride intake may cause dental fluorosis. All VI-FLOR* with Iron products: as with all products containing iron, parents should be warned against excessive dosage. The bottle should be kept out of reach of children.

Keep all VI-FLOR with Iron products tightly closed and away from direct light.

VI-FLOR Drops should be dispensed in the original plastic container, since contact with glass leads to instability and precipitation.

ADVERSE REACTIONS: Allergic rash has rarely been reported.

DOSAGE AND ADMINISTRATION:
Supplemental Fluoride Dosage Schedule (mg/day)*

Age	Concentration of Fluoride in Drinking Water (ppm)		
	<0.3	0.3-0.7	>0.7
2-wk-2 yr**	0.25	0	0
2-3 yr	0.5	0.25	0
3-16 yr	1.0	0.5	0

*From the American Academy of Pediatrics Committee on Nutrition statement Fluoride Supplementation: Revised Dosage Schedule. *Pediatrics* 63(1):150-152, 1979.
**The Committee favors initiating fluoride supplementation shortly after birth in breast-fed infants (0.25 mg F/day). In formula-fed infants, fluoride supplementation should be according to the fluoride content of the water used to prepare formula

PRODUCT	FORM	SIZE	FLUORIDE mg/dose
POLY-VI-FLOR 0.25 mg	Drops	50 ml Bottle	0.25
POLY-VI-FLOR 0.25 mg with Iron	Drops	50 ml Bottle	0.25
POLY-VI-FLOR 0.25 mg	Tablets	Bottle of 100	0.25
POLY-VI-FLOR 0.25 mg with Iron	Tablets	Bottle of 100	0.25
POLY-VI-FLOR 0.5 mg	Drops	50 ml Bottle	0.5
POLY-VI-FLOR 0.5 mg with Iron	Drops	50 ml Bottle	0.5
POLY-VI-FLOR 0.5 mg	Tablets	Bottle of 100	0.5
POLY-VI-FLOR 0.5 mg with Iron	Tablets	Bottle of 100	0.5
POLY-VI-FLOR 1.0 mg	Tablets	Bottle of 100	1.0
POLY-VI-FLOR 1.0 mg with Iron	Tablets	Bottle of 100	1.0
TRI-VI-FLOR 0.25 mg	Drops	50 ml Bottle	0.25
TRI-VI-FLOR 0.25 mg with Iron	Drops	50 ml Bottle	0.25
TRI-VI-FLOR 0.5 mg	Drops	50 ml Bottle	0.5
TRI-VI-FLOR 1.0 mg	Tablets	Bottle of 100	1.0

REFERENCES:
1. Hennon DK, Stookey GK and Muhler JC: The Clinical Anticariogenic Effectiveness of Supplementary Fluoride-Vitamin Preparations—Results at the End of Four Years. *J Dentistry for Children* 34:439-443 (Nov) 1967.
2. Hennon DK, Stookey GK and Muhler JC: The Clinical Anticariogenic Effectiveness of Supplementary Fluoride-Vitamin Preparations—Results at the End of Five and a Half Years. *Pharmacology and Therapeutics in Dentistry* 1:1-6 (Oct) 1970.
3. Hennon DK, Stookey GK and Muhler JC: Prophylaxis of Dental Caries: Relative Effectiveness of Chewable Fluoride Preparations With and Without Added Vitamins. *J Pediatrics* 80:1018-1021 (June) 1972.

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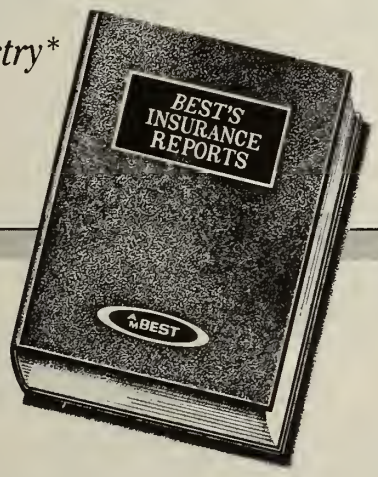

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Before prescribing, see complete prescribing information in SK&F CO. literature or PDR. The following is a brief summary.

* **WARNING**
This drug is not indicated for initial therapy of edema or hypertension. Edema or hypertension requires therapy titrated to the individual. If this combination represents the dosage so determined, its use may be more convenient in patient management. Treatment of hypertension and edema is not static, but must be reevaluated as conditions in each patient warrant.

Contraindications: Concomitant use with other potassium-sparing agents such as spironolactone or amiloride. Further use in anuria, progressive renal or hepatic dysfunction, hyperkalemia. Pre-existing elevated serum potassium. Hypersensitivity to either component or other sulfonamide-derived drugs.
Warnings: Do not use potassium supplements, dietary or otherwise, unless hypokalemia develops or dietary intake of potassium is markedly impaired. If supplementary potassium is needed, potassium tablets should not be used. Hyperkalemia can occur, and has been associated with cardiac irregularities. It is more likely in the severely ill, with urine volume less than one liter/day, the elderly and diabetics with suspected or confirmed renal insufficiency. Periodically, serum K^+ levels should be determined. If hyperkalemia develops, substitute a thiazide alone, restrict K^+ intake. **Associated widened QRS complex or arrhythmia requires prompt additional therapy.** Thiazides cross the placental barrier and appear in cord blood. Use in pregnancy requires weighing anticipated benefits against possible hazards, including fetal or neonatal jaundice, thrombocytopenia, other adverse reactions seen in adults. Thiazides appear and triamterene may appear in breast milk. If their use is essential, the patient should stop nursing. Adequate information on use in children is not available. Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma. Possible exacerbation or activation of systemic lupus erythematosus has been reported with thiazide diuretics.
Precautions: The bioavailability of the hydrochlorothiazide component of 'Dyazide' is about 50% of the bioavailability of the single entity. Theoretically, a patient transferred from the single entities of triamterene and hydrochlorothiazide may show an increase in blood pressure or fluid retention. Similarly, it is also possible that the lesser hydrochlorothiazide bioavailability could lead to increased serum potassium levels. However, extensive clinical experience with 'Dyazide' suggests that these conditions have not been commonly observed in clinical practice. Angiotensin-converting enzyme (ACE) inhibitors can elevate serum potassium; use with caution with 'Dyazide'. Do periodic serum electrolyte determinations (particularly important in patients vomiting excessively or receiving parenteral fluids, and during concurrent use with amphotericin B or corticosteroids or corticotropin[ACTH]). Periodic BUN and serum creatinine determinations should be made, especially in the elderly, diabetics or those with suspected or confirmed renal insufficiency. Cumulative effects of the drug may develop in patients with impaired renal function. Thiazides should be used with caution in patients with impaired hepatic function. They can precipitate coma in patients with severe liver disease. Observe regularly for possible blood dyscrasias, liver damage, other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving triamterene, and leukopenia, thrombocytopenia, agranulocytosis, and aplastic and hemolytic anemia have been reported with thiazides. Thiazides may cause manifestation of latent diabetes mellitus. The effects of oral anticoagulants may be decreased when used concurrently with hydrochlorothiazide; dosage adjustments may be necessary. Clinically insignificant reductions in arterial responsiveness to norepinephrine have been reported. Thiazides have also been shown to increase the paralyzing effect of nondepolarizing muscle relaxants such as tubocurarine. Triamterene is a weak folic acid antagonist. Do periodic blood studies in cirrhotics with splenomegaly. Antihypertensive effects may be enhanced in post-sympathectomy patients. Use cautiously in surgical patients. Triamterene has been found in renal stones in association with the other usual calculus components. Therefore, 'Dyazide' should be used with caution in patients with histories of stone formation. A few occurrences of acute renal failure have been reported in patients on 'Dyazide' when treated with indomethacin. Therefore, caution is advised in administering nonsteroidal anti-inflammatory agents with 'Dyazide'. The following may occur; transient elevated BUN or creatinine or both, hyperglycemia and glycosuria (diabetic insulin requirements may be altered), hyperuricemia and gout, digitalis intoxication (in hypokalemia), decreasing alkali reserve with possible metabolic acidosis. 'Dyazide' interferes with fluorescent measurement of quinidine. Hypokalemia is uncommon with 'Dyazide', but should it develop, corrective measures should be taken such as potassium supplementation or increased dietary intake of potassium-rich foods. Corrective measures should be instituted cautiously and serum potassium levels determined. Discontinue corrective measures and 'Dyazide' should laboratory values reveal elevated serum potassium. Chloride deficit may occur as well as dilutional hyponatremia. Concurrent use with chlorpropamide may increase the risk of severe hyponatremia. Serum PBI levels may decrease without signs of thyroid disturbance. Calcium excretion is decreased by thiazides. 'Dyazide' should be withdrawn before conducting tests for parathyroid function. Thiazides may add to or potentiate the action of other antihypertensive drugs. Diuretics reduce renal clearance of lithium and increase the risk of lithium toxicity.
Adverse Reactions: Muscle cramps, weakness, dizziness, headache, dry mouth; anaphylaxis, rash, urticaria, photosensitivity, purpura, other dermatological conditions; nausea and vomiting, diarrhea, constipation, other gastrointestinal disturbances; postural hypotension (may be aggravated by alcohol, barbiturates, or narcotics). Necrotizing vasculitis, paresthesias, icterus, pancreatitis, xanthopsia and respiratory distress including pneumonitis and pulmonary edema, transient blurred vision, sialadenitis, and vertigo have occurred with thiazides alone. Triamterene has been found in renal stones in association with other usual calculus components. Rare incidents of acute interstitial nephritis have been reported. Impotence has been reported in a few patients on 'Dyazide', although a causal relationship has not been established.
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JOURNAL OF THE ARIZONA MEDICAL ASSOCIATION

ARIZONA MEDICINE

MARCH 1988, VOL. XLV, NO. 3

Inquisitiveness — Not A Bad Trait

Marshall B. Block, M.D.

Although not given a formal education, my father, Charles made the most with what he was given and then some. He was never one to sit back and wait for things to happen. Rather, he was inquisitive and was always searching for new stimulation.

For instance, during one of my parents' recent visits to Phoenix, I had the occasion to take them out to dinner. Unfortunately I was paged to the hospital for an emergency and could not immediately join them. After leaving them at the restaurant, I returned approximately 20 minutes later and found my wife and mother amicably conversing at the table. My father, however was nowhere to be seen. Knowing my father's instincts I was immediately nervous and decided to track him down.

In a private room at the restaurant, a wedding was taking place. My father, long intrigued with religion (whether his or someone else's, it didn't matter) was sitting in the front row watching the ceremony. It never occurred to him that he wasn't invited! As quietly and as politely as I could, I nudged his arm and escorted him back to the main dining room. It turned out that a fellow colleague was being married and I was able to apologize to him at a later date. I told him that if the videotape of his ceremony contained a face that he did not recognize, it was probably my father's!

This "inquisitiveness" is a quality which we could all use. Although we are trained as "clinical" scientists, as one continues to practice, the "science" of medicine begins to wane a bit and the clinical aspects come to the forefront. Although new scientific information is injected into our practice modes, the scientific portion of our training becomes less sharp as we recognize that in caring for patients, more than hard facts are needed. The ability to communicate with a patient about matters which may be uncomfortable (death, sex, finances) or the mood to communicate on different levels with family, friends and children leads us further away from our scientific foundation. As we mature, we become less scientific than perhaps we should. This is a natural trend since much of what we do on a day-to-day basis has less to do with science than with human relations.

We must, however continue to be aware that as physicians we need also to function as scientists albeit "clinical" and continue to question and ask why things are occurring. By so doing we will not overlook the important physiological foundations of medical practice. As one colleague recently put it, "I am not concerned if my patients like me, I am just trying to make certain that I practice good medicine." Although at first blush this sounds harsh, it really is a truthful statement coming from a physician who does care but is trying to continue to keep the science portion of medicine in perspective. His patients do recognize his "caring" but more importantly they are also getting a balanced physician.

As my mother would say, "It wouldn't hurt!" for all of us to continue to have some of my father's inquisitiveness and maintain the happy ratio that gives being a physician such gratification. ■

Marshall B. Block, M.D.
Editor

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Perceptions of the OIG

(Editor's Note: The following is a reprint of the first half of a speech given by Richard P. Kusserow, inspector general of the U.S. Department of Health and Human Services. Mr. Kusserow presented these remarks to the annual meeting of the Federation of State Medical Boards of the United States. The second half of his remarks will be reprinted next month in Arizona Medicine, along with questions and answers that followed his speech.

It is particularly an honor for me to come to you and share our experiences and efforts in the Office of the Inspector General (OIG), Department of Health and Human Services, because I've really come to appreciate the work that you do. We're not unmindful of the fact that for a very large portion of the group that is assembled here today it is really a sacrifice, a personal sacrifice, to engage in this kind of work. That is, to be the protector for your profession and for the patients that depend upon your profession. And, in that respect, I think you'll appreciate why we're so thankful that you have worked so hard and have come so far in recent years in carrying out your own mission.

I think it's difficult in our role as the House Inspector General. We wear many hats. I'm both the internal and external auditor for some $348 billion in outlays each year for our department. I am also the inspector, program analyst, and investigator. My investigator hat includes criminal, civil and administrative investigations for the department's programs. We're extremely pleased that we have had great improvement in our statistical outcomes, however, I consider it more of a measure of failure than a measure of success. We have been increasing almost geometrically in output. We should not be vested in trying to get more stats, but vested in trying to get fewer stats because we make our department's programs run better, more efficiently and with greater effectiveness. But notwithstanding that as a measure of failure in one sense, we have had a tremendous increase. With our previous Inspector General in 1981, we had 165 felony convictions that our office had brought to and through the Federal justice system for those individuals that would engage in fraud and abuse against our department's programs. Last year, we had 1,055. That's roughly a 600 percent increase.

We are also the sanctioning authority for our health care programs. We're the ones that will exclude providers of health services or products from participating in Medicare or Medicaid. In that respect, we've also had a tremendous increase. We had only 39 such sanctions in 1981, and this last fiscal year we had 412. Roughly a 1,100 percent increase.

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Perceptions

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In dollar returns to the Federal taxpayer and to our programs in the form of fines, savings restitution and recoveries, we went from $166 million in 1981 to over $5.3 billion this year—a 3,500 percent increase.

In one measure, it seems that we can go back to the Congress and say that we're cost effective. But, at the same time, it is also a statement that our programs haven't reached the point where there are fewer opportunities for (and fewer people that engage in) fraud, waste and abuse. It's a double-edged sword in this regard.

In 1981, when we started getting into the health care arena, it became clear that we were depending upon you. We were depending upon the licensure process almost totally for insuring that we had qualified practitioners in our programs. In 1965, when Medicare and Medicaid came into being—particularly Medicare—it set forth the fact that there were two criteria for a health provider getting a provider

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Richard P. Kusserow was nominated as inspector general of the Department of Health and Human Services by President Reagan in April of 1981 and confirmed by the Senate in June.

As inspector general of the Department of Health and Human Services, he is charged with the statutory responsibility to ferret out fraud, waste, abuse and inefficiency in the world's largest agency. This department has some 250 health and human services programs and a budget of $361 billion which represents one-third of the federal budget. Kusserow directs a staff of 1,200 auditors, inspectors, program analysts and investigators who recorded $5.3 billion in fines, savings, restitutions, recoveries and settlements in the last year. This represents a 3,000 percent increase over 1981 levels. More than $15.9 billion in such savings have been realized during Kusserow's tenure. In the same time frame, convictions resulting from his investigative staff rose from 165 to over 1,055, a 600 percent increase. Additionally, he has increased administrative sanctions by 1,000 percent against health providers and suppliers. He has "kicked out" of the Medicare and Medicaid programs over 1,300 individuals and entities for abusive or fraudulent behavior against the programs or beneficiaries. Kusserow is currently serving a second term as the vice chairman of the President's Council on Integrity and Efficiency (PCIE). The PCIE, created in 1981 by President Reagan, provides cohesive leadership to government-wide activities to reduce fraud, waste and abuse in federal programs and operations. Kusserow has responsibility for coordinating and tracking all government-wide inspector general projects; managing the preparation of the president's semiannual report on the accumulated accomplishments of all inspectors general; coordinating efforts with the President's Council on Management Improvement; and serving as liaison for all inspectors with the Office of Management and Budget. He earned his bachelor's degree in political science from UCLA, master's degree in government from California State University at Los Angeles, followed by postgraduate work at Southern Methodist University and John Marshall University Schools of Law. Kusserow served in the United States Marine Corps and was discharged as a captain. He was an intelligence officer with the Central Intelligence Agency (CIA) before moving to the Federal Bureau of Investigation (FBI) in 1969. As an FBI agent, he worked in Pennsylvania, Washington D.C., West Virginia and Chicago. He acted as the coordinating supervisor for nine squads of agents constituting the Chicago FBI Organized Crime program preceding his appointment as inspector general. He was twice elected president of the National Association of Federal Investigators and is an active member of the Society of Former FBI Agents, Association of Government Accountants, International Association of Chiefs of Police and the American Society of Industrial Security. He has lectured widely and authored numerous articles on innovative investigative and management techniques on fraud and corruption in government programs. He is author of a book entitled "Management Principles for Asset Protection."

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(PERCEPTIONS, continued from page 4)
number for billing in the system. He was first being duly licensed and second, had never been disciplined in such a way that would have removed his practicing privileges.

We had some concerns because we were buffeted by a number of different problems that we were encountering with Caribbean schools, with schools in the United States that were selling credentialing. Additionally, as we began to prosecute and sanction more and more providers, we realized that we were beginning to see that many of these individuals had prior problems. So, we wanted to see what, in fact, was out there that we were depending upon. Therefore, we did a study on medical licensure and discipline in the United States. We worked very closely with you in trying to understand the obstacles that you were confronted with in carrying out your responsibilities.

The thing that astounded us most is how you were able to function at all with the burdens that were placed on you; the lack of, in many, many areas of this country, funding and staffing. Also, the very heavy due process requirements that were placed upon your operations. It became clear to us that many of these obstacles were unnecessary. And when we issued our report, that's basically what we stated. We focused in on what it is that we can do to make the system run more efficiently, what it is that we can do to lubricate and strengthen the whole licensure and discipline process in the United States. I used to teach constitutional law and it says very clearly in the 10th and 11th Amendments of the Constitution of the United States that the protection of the health and welfare of the people of the several states are with the states and not with the Federal government. I do not believe that this is a federal responsibility, and whatever problems exist there should be remedied through the states.

As a corollary to that, I believe we should not have people like myself, who are the least competent, questioning the competency of physicians. It is the professionals themselves who must, in fact, be involved in this process. And it's with that strong bias that I have testified at seven different hearings relating to this subject and advocated that there should not be, certainly in the office of Inspector General, any clearinghouse; that it should not be the office of Inspector General that brings charges against physicians or other practitioners for questions of competency.

Unfortunately, one of the things that we did observe in our review of medical licensure and discipline is that in the matter of discipline, the majority of the cases come from those parts of the community that are the least competent to question the competency of physicians. That is, advocacy groups and police agencies such as our own or local authorities. There is a relative silence from the professional community. And in examining the causes, it became clear that one overriding issue was the fear of being sued for bringing forth information and a lack of confidence as to whether or not the information being provided would be treated in a proper fashion.

Another point that should be mentioned is that the practitioner community thinks it's their responsibility to bring charges against a fellow physician in order to have it properly resolved. I think this stems from the fact that we've had over a thousand years in our Anglo-American and judicial system, and a concept that we are all responsible as policemen in our society and that we don't have the professional constabularies who have that responsibility.

When you're talking about problems involving physicians, another physician is going to obtain this information most likely through hearsay. As we know, there are few exceptions to the hearsay rule, and you can't testify from hearsay. You can only testify from firsthand experience. What you may have is Physician B receiving patients that have come from Physician A, and in reviewing the treatment plan for whatever formality is being treated there's some question raised in physician B's mind as to how that was handled. That physician, in many cases, wants to alert authorities, but doesn't know how to go about it and doesn't know whether or not the facts are sufficient and clear enough in his own mind that he feels confident to really bring charges. One of the things that we've tried to emphasize in our own work in this arena is telling the physicians they can have total anonymity when they talk to us. We are not interested in having them testify against a fellow practitioner but only to alert us as to what they think is going on. Let us go through record searches to see if we can sustain the suspicions through our own investigation. We will be the ones that bring testimony and not the individual physician.

We've looked around the country and again we asked questions about physicians that say their last settings before becoming licensed were in the hospital. We asked questions from supervising physicians about how well the system is working when they encounter incompetency problems or conduct problems. And

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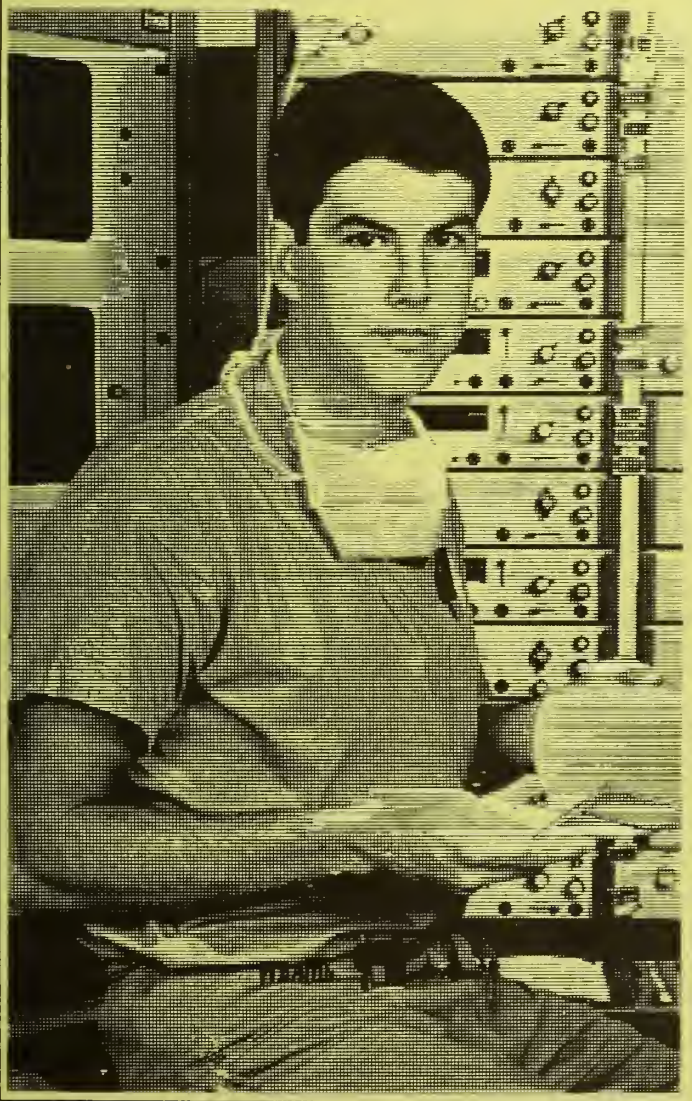

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Perceptions

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the university came back, an almost wrenching kind of experience, with yes, they do encounter problems like that. They feel greatly constrained in reporting, calling the shots the way they actually see them, because again they fear being sued. In fact, the appropriate remedy in most cases is really to ask the intern or resident not to come back next year. Unfortunately, that means that they will go on someplace else and repeat their performance, their bad performance, and have the same thing happen even a third time. Then they go to a licensing board, without anything on their record to indicate that they're really not qualified to become a practicing physician in the United States. So we begin to see a whole potpourri of problems in the system, and we work very hard to see if we can bring it to the floor.

One thing that I most often recall from the Bible is in the Book of Revelations. You really can't be a prophet in your own land. I somehow feel that you are suffering from that kind of a situation. There is nothing that we raised that you have not raised individually or collectively in your own states or nationwide. Somehow you aren't hated as much when the Inspector General comes out and says basically the same thing you are saying and then people tend to listen. It seems that there's a lot of activity and perhaps we've provided some measure of a catalyst for the changes that have, I think, certainly improved the ability of you people to do your job in aggregate. We are very pleased about that.

There has been a lot of legislative activity through the last three sessions of Congress with regard to what we are going to do about these problems. I've found myself the only voice in the Federal government that is actually speaking for the Congress. Nobody else seems to have a vested interest in the subject. My concern is that three sessions ago it looked very much like the Congress was going in with a knee jerk reaction to create a national clearinghouse and that this clearinghouse would have obligations to actually carry out what I thought was your responsibility and your mission to the Federal government. Through a lot of hard work, we've been able to check that and put it into proper perspective and say it's not really national law that's needed here as much as it is support in states to support in turn your role.

We did have the Wyden bill passed in the Congress, better known as the Health Care Quality Improvement Act. Again, the only government official that testified on that bill was myself because very few other people seemed to have even a rudimentary understanding of the issue. We were very pleased with the way that bill came out.

There is one feature of the bill that I don't care about and testified against. I struggled very hard to convince Ron Wyden not to include in the bill the requirement to submit reports on medical malpractice and payments. I don't know what our office could ever do with that information. I'm not sure of its relevance and don't know how it could be used as a predictor of future conduct or behavior. In trying to argue the case, I was hoping to compromise it by taking California's rule of a $30,000 threshold, but we even lost on that point and it even comes down to a minimal settlement as being something that's reportable. But the other features of the bill look good. I think it's a bill that preserves the basic principle that the health and welfare is with the states and not with the Federal government. That what you're really talking about is ways in which you can build incentives into the system to have people report.

The one basic principle that is necessary in any kind of a reporting system is an affirmative duty for everyone, that is every physician, to bring forth to a duly authorized investigative authority issues that would raise questions about somebody else in the same field. But you cannot create that kind of an affirmative duty without certain protections. There are two kinds of protections that must exist there and which we've advocated very strongly. First, protection from being sued, if you bring that information in good faith, and second, that you afford due process to the accused. What I mean by that is going back to our long tradition of Anglo-American jurisprudence. We all have an affirmative duty under the law to report information about a crime that has been committed. If you see somebody burglarizing your neighbor's home, you have an affirmative duty to report. Failure to report could constitute a crime in itself, resulting in a felonny. And, it must be to a duly authorized authority. In that case, it's the police department.

It's not an appropriate reporting mechanism for you to get on top of a roof and shout to all the neighborhood that Joe Schmekatella is a burglar. That's not appropriate. It's not appropriate that you go to the newspapers and accuse him. You do it through an appropriate investigatory authority that will afford due process. The same thing is true here. That is if you create an affirmative duty, it should be to a duly autho-

rized board. This means you people. You can then afford the appropriate due process to assure against error, bad faith, maybe upon the reporting individual, and to make sure that the matter is resolved in a proper fashion.

And I think the basic principles are coming through in the Wyden bill. The Medicare-Medicaid Patient Program Protection Act, which is before Congress and looks promising that it will pass in this session, also carries forth those basic principles. I think it is a good sign, and I think it also shows a recognition of the fact that this body is the appropriate one to deal with these problems.

With regard to the clearinghouse, I will tell you it's been brought to my attention very clearly that you have an interest in the clearinghouse that is being considered by the task force set up by HRSA and which I'm part of. Let me just tell you what my basic feelings are about this clearinghouse in a little bit more depth than what I just previously alluded to. In many respects, they wanted to set the clearinghouse up as a function to be contracted out—contracted out of the OIG. I said, no, I should not be part of that process, even though I'm the one who would interface with the process more than anybody else in the department. I feel it's inappropriate for me to have it, and we finally agreed it should go to HRSA. I wanted to be sure that we would not be creating a new Federal program. That this would not be the beginning of a great new empire because I think that's counterproductive to this whole concept. It should be a facilitator to good communication and nothing more.

The concept of having an advisory board to this contracted clearinghouse is my idea as a way once again to insure that the contractor would only act as a facilitator for the program and would not make policy. The advisory board that would govern the clearinghouse would, in fact, be the policy maker and insure that the program is operating to the letter of the law.

I will also tell you that I believe that there should be a strict construction approach as to what that clearinghouse would do. We should not be allowed to spill over and to broaden out beyond what the original intent was, and I would like to make sure that that does not happen. I will, therefore, focus my energies along these lines. For those who might be interested, our next meeting is April 28—which is next week. The HRSA staff right now is preparing drafts of the RFP and the regulations. I will tell you that they're still pretty much in the outlining stage. The source statement or the clearinghouse has already been published. The issue being tackled by the advisory group at the present time is what practitioners should be included in the bank for malpractice actions. There is a General Counsel dispute.

As to what should be included in the malpractice actions, once again I will tell you that my advice is to take the strictest, constructionest approach on that subject. I'm not pleased with that concept and I don't know how useful it is. I will be doing a study on that once it's implemented to see how effective it is in providing appropriate information to the people that can act on it. I'm not too sure what that would be.

We're also looking at H.R. 1444 which is the Medicare-Medicaid Patient Program Protection Act. It also has a clearinghouse function. One of the ironies is that this omnibus bill has been floating through the last three sessions of the Congress, getting refined at each stage. The fact is it actually is becoming a better bill at each stage. It had carried the clearinghouse concept. What Ron Wyden did is to capture much of that and slip a bill in which more than anything else tells you that he is really a competent Congressman. I've never seen anybody as unabashed about calling me about more things than Ron Wyden in Oregon. He is really an aggressive Congressman and as far as I'm concerned the people in Oregon have got somebody that is a rising star in Congress.

But the fact remains that H.R. 1444 is the main vehicle that's carrying most of the correction language. It's one bill that I think you people would feel far more comfortable with than with the Wyden bill because it is more limiting and does not include the malpractice feature. It involves a clearinghouse that transcends the physician. It goes into a lot of other allied professions. We're not too sure what it means or how it will work. We're studying that and the implications of what happens if H.R. 1444 passes in view of the clearinghouse that's currently being set up.

(To be continued next month.)

Kevin Walker Promoted

Kevin Walker, former Assistant Executive Vice President of the Arizona Medical Association, has been promoted to Director of the Department of Political Action in the Division of Political Education/AMPAC in its Washington, D.C., office.

Walker, who left ArMA two years ago to become the American Medical Association's Director of State and County Relations, succeeds Jack Hotaling, who has been named Assistant to the Director of Membership. ■

Children's Research Center at the University of Arizona

The new Children's Research Center at the University of Arizona has been established to help meet several major objectives. The medical/scientific "explosions" currently occurring in areas such as genetics, immunology, and molecular biology, combined with the realization that major medical problems still face children has been a major impetus for increasing multidisciplinary research efforts related to the numerous illnesses and diseases from which children still suffer. However, the further development of research programs in these and other areas will be impossible or, at best, extremely difficult without additional space.

The rapid growth of the University of Arizona College of Medicine over its first twenty years has been accompanied by the recruitment of numerous outstanding investigators. This, however, has rapidly exhausted available space. The continued successful growth of the College of Medicine as a leading medical institution necessitates the addition of extensive new space facilities. The Children's Research Center is one part of the efforts currently planned to meet these space needs.

The Children's Research Center was established in 1986 as a major focus for increasing the research and educational activities within the College of Medicine, the Arizona Health Sciences Center, in general, and Main Campus. Obviously, the end result of these activities is what is most important, namely the provision of better care for children, prevention of illness and accidents, and cures for many life-threatening illnesses and diseases.

The goals of the Children's Research Center include:

- Coordinate, focus, foster, and facilitate multidisciplinary research related to children's health
- Generate a continuing high level of interest and support for research related to children
- Develop long-range plans for enhanced support of scientific-/medical research activities related to children's health
- Enhance the education of all health care personnel (medical students, residents, fellows, nurses, etc.) through the development and/or expansion of research programs and addition of new faculty
- Expand research training progams, thereby facilitating the training of future researchers
- Enhance patient care by the addition of new faculty with additional expertise in various medical areas and by the expansion of research programs related to diseases of children
- Facilitate the rapid application of research observations to patient care

In order to achieve these goals, an Advisory Board of lay leaders in Arizona, and from other states, was established. This Board, headed by Louise Thomas of Tucson, has assumed a major role in determining the extent of the various projects, publicity, construction, and fund-raising. A major facility will be built to house research laboratories and office space. In addition to individual research laboratories, the Children's Research Center facility will include multiuser laboratories, specialized labs, conference rooms, and space for predoctoral and postdoctoral students and Fellows. The Center is also seeking to establish additional Endowed Chairs and Professorships, a general Research Endow-

(Continued on page 20)

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College of Medicine - 1978

MARICOPA

Barbara A. Cooper, M.D.
Hematology, Oncology
5310 West Thunderbird Road
Suite 302, Glendale
West Virginia University
School of Medicine - 1980

William J. Fleischaker, M.D.
Family Practice, Physical
Medicine & Rehabilitation
1010 East McDowell Road
Suite 203, Phoenix
University of Oklahoma
College of Medicine - 1979

Ira L. Goodman, M.D.
Ophthalmology
5757 West Thunderbird Road
Glendale
Loyola University of Chicago-
Stritch School of Medicine - 1974

Finn O. Gunderson, M.D.
Orthopedic Surgery
4616 North 51st Avenue, Phoenix
University of Wisconsin
Medical School-Madison - 1959

Leonor A. Maderazo, M.D.
Anesthesiology
P.O. Box 39179, Phoenix
Faculty of Medicine and Surgery-
University of Santo Tomas - 1962

Gustave A. Matson III, M.D.
Obstetrics & Gynecology
5620 West Thunderbird Road
Glendale
University of Utah
College of Medicine - 1982

Manfred D. Muenter, M.D.
Neurology
13400 East Shea Boulevard
Scottsdale
Medical Faculty of Freien
University-Berlin - 1958

James A. Peterson, Jr., M.D.
General Surgery
755 East McDowell Road, Phoenix
University of Nebraska
College of Medicine - 1972

James A. Singer, M.D.
Gastroenterology and Internal
Medicine
6036 North 19th Avenue
Suite 309, Phoenix
State University of New York-
Buffalo School of Medicine - 1972

Steven H. Turkeltaub, M.D.
Plastic Surgery and Hand Surgery
3225 North Civic Center Plaza
Scottsdale
Boston University School
of Medicine - 1979

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Joseph C. Heinlein, M.D.
Pediatrics
9302 East 22nd Street, Tucson
University of Nebraska
College of Medicine - 1957

Fred H. Ovrom, M.D.
Internal Medicine
P.O. Box 12650, Tucson
University of Iowa
College of Medicine - 1981

Steven D. Vig, M.D.
Internal Medicine
P.O. Box 12650, Tucson
University of Wisconsin
Medical School-Madison - 1979

YAVAPAI

William E. Merrell, M.D.
Internal Medicine
1011 Ruth Street, Prescott
University of Arkansas
College of Medicine - 1973

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Massachusetts Medical Society v. Dukakis

Denial of Cert: What It Means For Arizona Physicians

On October 13, 1987, all eight justices currently sitting on the U.S. Supreme Court agreed to deny the petition for "writ of certiorari" in an appeal from the Massachusetts Medical Society's case against Governor Dukakis and state medical licensure officials. *Massachusetts Medical Society v. Dukakis,* U.S. Slip Opinion No. 87-173. The effect of this "denial of cert" is to leave standing the decision of two lower federal courts, **a statute requiring that physicians accept assignment when treating Medicare patients is law in the Commonwealth of Massachusetts.** In addition, it offers a rational basis for speculation as to the decision's impact on physicians practicing medicine in other states.

The Massachusetts Background

At issue was Chapter 475 of the Massachusetts Acts of 1985, providing that the Board of Registration in Medicine

> *"shall require as a condition of granting or renewing a physician's certificate of registration, that the physician, who if he agrees to treat a beneficiary of health insurance under Title XVIII of the Social Security Act, shall also agree not to charge to or collect from such beneficiary any amount in excess of the reasonable charge for that service as determined by the United States Secretary of Health and Human Services."*

"Balance billing" is therefore prohibited under the statute: physicians receive 80% of the established reasonable charge from Medicare, collecting the remaining 20% (but no more) directly from the patient.

In affirming the decision of the Massachusetts District Court, Judge Breyer of the First Circuit Court of Appeals held that: (1) the statute was not preempted by the federal Medicare Act, and (2) the statute did not improperly deprive doctors of "liberty" to practice their profession. *Massachusetts Medical Society v. Dukakis,* 815 F.2d 790 (1st Cir. 1987). The rationale of both the district court [*Massachusetts Medical Society v. Dukakis,* 637 F.Supp. 684 (D.Mass. 1986)] and the court of appeals centered on the state's "rational relation to a legitimate purpose" in its desire to contain medical costs for the elderly. The medical society's counter-argument—that the licensure statute did not focus, as it should have, primarily on physician "fitness or capacity to practice"—was unsuccessful.

What It Means To Doctors Elsewhere

Traditionally the states themselves have set requirements for licensure of medical professionals within their own borders, and the existence of Medicare as the federal health insurance program for the nation's elderly is unlikely to change that situation. The Supreme Court's denial of cert in the Massachusetts case reflects a long-standing reluctance on the part of the nation's highest court to encroach on matters traditionally belonging to the states under the Tenth Amendment.

So what are the legislatures of other states likely to do, in light of the Massachusetts decision? Technically, the First Circuit's decision sets precedent only for states or territories within that circuit's jurisdiction: Maine, Massachusetts, New Hampshire, Rhode Island and Puerto Rico. Any or all of these could enact a statute exactly as broad as (or narrower than) the Massachusetts one, and the legislation would essentially stand.

But what of other federal court jurisdictions? Given the high court's refusal to interfere in the Massachusetts legislation, this much seems obvious: more than likely, **any** state legislatures which enact similar statutes no broader than the Massachusetts one would find their legislation withstanding court challenges.

A Possible Course of Action In Other States

The reasoning in the two lower courts' opinions suggests that the judge in each weighed heavily the concerns of Massachusetts' legislators regarding the state's Medicare patients and their affordable access to medical treatment from Commonwealth doctors. Concerns for the old and sick who might also be impoverished—*largely unable to afford balance billing*—seem to have been the legislation's impetus. The perceived needs of the **elderly** under the Medicare reasonable charge determinations were weighed against **physicians'** desire to be permitted balance-billing. In Massachusetts, the elderly won this theoretical **either-or** contest.

A possible course of action for medical societies in states outside the First Federal Circuit (at least, states in which no definitive similar statute has already been enacted) might well be in terms of a *possible preventive-measure.* Members of the state medical societies may wish to sponsor

jointly a resolution stating that physicians who elect non-participation Medicare status do so **in order to use case-by-case discretion on acceptance of assignment, relative to individual patients' ability to pay.**

Such a resolution, carefully drafted by a state medical society's counsel and directed with finesse toward appropriate members of a legislature in session, could conceivably reduce the likelihood that state-level representatives would reach a conclusion similar to that of the Commonwealth of Massachusetts. Instead of an **either-or** weighing of physicians' practice-management decisions VERSUS Medicare beneficiaries' needs, perhaps requirements of **both** groups can be actualized in this fashion without an across-the-board sacrifice of one at the expense of the other.

MGMA members may wish to discuss the possibilities of this course of action with physicians in their group practices.

Medical Coalition Proposes Plan To Mitigate Malpractice Crisis

A radical proposal to resolve medical malpractice claims more fairly and efficiently has been unveiled by the American Medical Association and 32 national medical specialty organizations (The AMA/Specialty Society Medical Liability Project).

The proposal calls for a fault-based administrative system, under the jurisdiction of strengthened state medical boards or a new state agency, which would totally replace the existing court-/jury system. It is proposed at this time only as one promising alternative to the tort system — an alternative that needs to be tested in one or more states before it can be proposed broadly as a solution to the continuing problem of medical professional liability.

"Organized medicine is not abandoning the court system or traditional tort reform, but we have an obligation to patients and physicians to experiment with different approaches to medical professional liability," said James S. Todd, M.D., Senior Deputy Executive Vice-President, speaking on behalf of the AMA/Specialty Society Medical Liability Project, an umbrella group which has been studying possible long-range solutions to the continuing medical malpractice problems.

"We have worked for over a year with a unique coalition of lawyers, physicians and public experts—inside and outside of organized medicine—to design what is above all a fair system—fair to the patient, the physician and the public. We believe that more patients injured by medical negligence will be compensated under this plan, but that fewer dollars will be spent on meritless claims and unnecessary transaction costs," Dr. Todd explained.

The proposed system has three basic parts: (1) a claims resolution function; (2) a credentialling and disciplinary process; and (3) a codification of the legal elements of medical liability. All three aspects are to be administered by a revamped state medical board or a new state agency, whose members are appointed by the governor. Physician members would play an important role on the Board, but would not be in a majority.

The Claims Resolution Function

Rather than through a court action before a jury, complaints of medical malpractice will be presented to an expert administrative agency where an initial screening will be performed by experienced claims reviewers who have authority to examine medical records and to interview the parties. It is believed that most claims will be dismissed or settled at this stage. Throughout the administrative process, lawyers from the agency's office of general counsel will be provided at no cost to any claimant who wishes such representation. If the claim is not settled, it will be assigned to a hearing examiner with broad authority to conduct a full and prompt hearing on the merits of the claim. The hearing examiner's decision will be subject to review by the Board, which will have discretion to award fees and costs incurred in the appeal against the losing party.

Keith White, M.D., the American College of Obstetricians and Gynecologists' representative on the Steering Committee of the AMA/Specialty Society Medical Liability Project, stated, "As the reviewers and examiners gain experience and expertise they should be better able than a jury to evaluate medical negligence claims and, for the first time, the decision-making process should be consistent in both liability determinations and the size of damage awards. The system also should be quicker than the current system and thereby save both plaintiffs and defendants the substantial expense incurred in litigating cases for years in a state court. Of equal significance, patients will be able to enter the system and obtain compensation without finding and paying for a lawyer themselves."

The Credentialling and Disciplinary Functions

All settlements and awards will be reported to the investigative branch of the agency for screening with other malpractice or disciplinary reports to determine if a pattern of substandard conduct exists. In addition, all health care entities will be required to conduct periodic physician performance credentialling and to report to the Board any conclusion that a physician's overall performance has been substandard. Insurers will be required to report cancellations and failures to renew for reasons related to competence. All of this information must be maintained in a clearinghouse accessible to those who conduct professional review activities, and certain credentialling agencies, like hospitals, will be required to check with the clearinghouse on a regular basis. "Linking the claims process with the medical board's separate disciplinary system will enable the board to oversee more effectively physicians' performance," said Paul Nora, M.D., representing the American College of Surgeons.

The Legal Elements of Medical Liability

The rules governing standard of care based on custom and locality would be abolished in favor of a standard that focuses on whether the challenged actions fall within a range of reasonableness, to be determined by reference to the standards of a prudent and competent practitioner in the same or similar circumstances. A variety of factors would determine the range of reasonableness, including the expertise of and means available to the health care provider, the state of medical knowledge, the availability of facilities and access to transportation and communications facilities.

The liability standard would also be modified to allow recovery if the physician's negligence was a "contributing factor" in causing the injury, even if the physician was less than 50 percent at fault. The informed consent doctrine would be codified under the current "minority" rule which requires that the adequacy of the disclosure should be measured from the perspective of the reasonable patient. Non-economic damages (and punitive damages) would be capped at an amount that is tied to a percentage of the average annual wage in the state. Economic damages would be awarded under a series of guidelines designed to ensure that those damages represent a realistic "replacement cost." The rule of joint and several liability would be abolished so that defendants would be liable for damages only in proportion to their actual liability. In addition, any award of future damages, where the present value of such damages exceeds $250,000, would be made in accordance with a periodic payment schedule. Finally, damages generally would be reduced by collateral source payments.

"This is the first comprehensive proposal for a radically new system for compensating victims of medical negligence and reducing the incidence of substandard care" says Dr. Todd. "The Medical Liability Project invites discussion and debate of the proposal by all interested groups and hopes that some state will put the proposal to the test soon." ■

Long Term Health Care Facilities Directory Available

The Arizona Department of Health Services (DHS) has just published the "1988 Directory of Licensed Long Term Health Care Facilities." This guide lists all long term care facilities licensed by DHS, including information about services and fees for home health agencies, supervisory care homes and nursing homes.

When a family member or a loved one can no longer live independently, knowledge of available long term care facilities and services will help to make informed choices for care. This directory is designed to identify those activities of daily living which can be done independently and those which require help from someone else. This information can assist in determining the kinds of services and care needed.

Also provided is information on how to find other supportive services that exist reasonably close to home. Such services include adult day care, home-delivered meals, group dining, visiting services, transportation, etc.

A free copy of the directory is available by calling DHS, Long Term Care at 220-6409 in Phoenix or 628-5870 in Tucson.

WHY AMA?

While the AMA endorses competition in health care delivery that eliminates excess cost without compromising quality, the AMA actively opposes any legislative initiatives that would reduce quality of medical services. AMA leadership in making high quality, cost effective health care available to the American public: it's one more good reason why you should be a part of the AMA.

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Physicians in the News

The Honorable Charles H. Percy and Dr. Taylor and his daughter, Susan, look on as Mrs. Taylor joins Richard Hill, M.D., Mayo Clinic Scottsdale, in unveiling the auditorium plaque honoring Ashton B. Taylor, M.D.

A dedication ceremony for the Mayo Clinic Scottsdale continuing education auditorium was held Saturday, January 16, honoring Mayo Clinic alumnus, Ashton B. Taylor, M.D., Phoenix.

"We are proud to call Ash one of ours as a former Mayo fellow, member of the Mayo Clinic staff and a member of the Board of Trustees of the Mayo Alumni Association," said W. Eugene Mayberry, M.D., at his first public event as chairman of development.

"One of the professional loves of my life has been my association with Mayo Clinic," said Dr. Taylor. Dr. Taylor has had a distinguished medical practice in the Valley for the last 32 years.

The honorable Charles H. Percy spoke as a close friend of the Taylor family, reminiscing about their long-time friendship.

Mrs. Taylor joined Richard Hill, M.D., Mayo Clinic Scottsdale chairman of the board, in unveiling the nameplate and plaque honoring Dr. Taylor's distinguished practice of medicine and his active support of continuing medical education.

Mark H. Zimmerman, M.D., Lake Havasu City, orthopaedic surgeon and medical director of the Havasu Arthritis and Sports Medicine Institute, has been selected as an Academy Fellow to the American Academy of Orthopaedic Surgeons.

There are 10,860 active Fellows in the Academy.

To become a Fellow, one must complete medical school training—usually four years—followed by five years of orthopaedic training, then three years of private practice. He must also be a board-certified in orthopaedic surgery.

A formal ceremony to induct new Fellows into the America Academy of Orthopaedic Surgeons was held in Atlanta, Georgia in February.

Jeffrey Edelstein, M.D., has successfully completed the final requirements for membership and has been inducted as a member of the American Society of Ophthalmic Plastic and Reconstructive Surgeons.

With the acceptance last fall of his thesis, "Medical Palpebral Tendon Repair for Medial Ectropion of the Lower Eyelid," Dr. Edelstein then had to successfully complete oral and written examinations. He passed both exams in December and was accepted into full ASOPRS membership.

(Continued on page 20)

Edelstein
(Continued from page 19)

Jeffrey Edelstein, M.D.

ASOPRS, founded in 1969, is a specialty society dedicated to excellence in cosmetic and reconstructive eye plastic surgery. During its 18-year existence, it has grown to include approximately 250 members throughout the U.S. According to Dr. Edelstein, many recent advances in this field are directly related to a greater awareness and application of anatomic concepts developed by many of the members of the society.

Dr. Edelstein is also Board certified, a member of the American Academy of Ophthalmology and a graduate of the Medical College of Wisconsin. He has staff privileges at Desert Samaritan, Mesa Lutheran, St. Luke's and other Phoenix-area hospitals.

Children's Research Center
(Continued from page 10)

ment, and a Visiting Lectureship Endowment.

The Children's Research Center, one of the seven "Centers of Excellence" at the College of Medicine, is also a major component of the new Century II fund-raising campaign for the University of Arizona. The building of the facility for the Center, as well as the establishment of research endowments, will allow the Center to become a leading research institution in the area of child health, facilitate the recruitment of additional faculty, and encourage the establishment of multidisciplinary research efforts related to pediatric illnesses and diseases.

The Medical Director for the Center is Lynn M. Taussig, M.D., who also is Professor and Head of the Department of Pediatrics at the College of Medicine.

Lynn M. Taussig, M.D.
Professor and Head
Department of Pediatrics

Vincent A. Fulginiti, M.D.
Acting Dean
College of Medicine
University of Arizona

AMA Announces Health Reporting Conference

The American Medical Association's Division of Television, Radio and Film Services is again sponsoring the Health Reporting Conference for physician broadcasters, medical reporters and spokespeople. The conference will be held in New Orleans at the Hyatt Regency from April 21-14, 1988.

Over the past seven years, hundreds of physicians have received speakers training, broadcast training and gone back to their local communitites to become medical society spokespersons, on-air reporters and regular guests of talk shows.

The conference is a unique blend of skills-building and substance, enabling participants to learn hands-on presentation techniques that are specifically related to medical reporting and representation of medical and health-care organizations and issues.

Attendees have the opportunity to attend optional workshops in a wide variety of areas; they hear from top broadcast physicians in the country, network executives and working broadcast journalists, plus speech coaches and writers—all professionals in the areas of broadcasting and platform speaking. The format is variety to provide lecture and hands-on courses; panel discussions and one-on-one critiques round out the curriculum.

For further information, contact program coordinator Jill Stewart, (312) 645-5414. ■

Office of Vital Records Announces New Hours

The Office of Vital Records at the Arizona Department of Health Services (DHS) has announced new office hours. Effective Monday, January 11, the office will be open to the public from 8:00 a.m. to 5:00 p.m., Monday through Friday. The Office of Vital Records is located at 1740 West Adams, Phoenix, west entrance.

These new hours will replace the present 7:30 a.m. to 4:30 p.m. schedule. The change is being made to serve the public better.

The Office of Vital Records maintains and operates a statewide system to register all birth, death, and fetal death records for the state of Arizona. The office currently has over 2,700,000 of these records on file. During 1987 more than 45,000 over-the-counter applications for records were handled by this office.

For more information about services offered by the DHS Office of Vital Records, call 255-1072.

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Oat Bran as a Cholesterol-Reducing Dietary Adjunct in a Young, Healthy Population

KURT V. GOLD *and* DENNIS M. DAVIDSON, MD, *Irvine, California*

In a study to examine the effects of dietary oat bran on serum lipids, subjects who ate two oat bran muffins a day for 28 days showed a 5.3% reduction in serum total cholesterol and an 8.7% reduction in low-density-lipoprotein-cholesterol levels, while no changes were noted in subjects consuming wheat or mixed wheat and oat bran muffins. Similarly, those who ingested oat bran muffins showed an 8.3% reduction in serum triglyceride values as contrasted with an overall increase of 6.4% in the other groups combined. These findings suggest that oat bran taken daily can significantly lower serum cholesterol and triglyceride levels in a young, healthy population.

(Gold KV, Davidson DM: Oat bran as a cholesterol-reducing dietary adjunct in a young, healthy population. West J Med 1988 Mar; 148:299-302)

Cardiovascular disease is the leading cause of death in the United States.[1] Elevated levels of serum total cholesterol and low-density-lipoprotein cholesterol (LDL) and low levels of high-density-lipoprotein cholesterol (HDL) have been recognized as risk factors in the development of atherosclerosis and coronary artery disease.[2] It has been shown that reducing the levels of blood cholesterol and LDL cholesterol decreases the risks for coronary artery disease.[3,4] Several dietary factors have been associated with serum cholesterol and LDL-cholesterol levels, including the amount and quality of fat, dietary cholesterol, fiber, and carbohydrate intake.[5] With increasing evidence that atherogenesis begins early in life,[6] the rationale for cholesterol-reducing dietary modifications published years ago[7] becomes particularly relevant to younger segments of our population. This study adds to the work of others showing cholesterol-reducing properties of certain dietary fibers and specifically evaluates oat bran as a hypocholesterolemic agent in healthy young adults.

Dietary fibers, which have been defined as all "nondigestible cell wall components," can be subdivided into water-soluble and water-insoluble components.[8] Water-soluble fibers such as those abundant in oat bran, beans,[9] guar gum,[10] and fruit pectin[11] have been reported to lower serum cholesterol levels. The cholesterol-reducing effect of water-soluble fiber has been further shown to selectively lower LDL-cholesterol levels, sparing or actually raising the cardioprotective HDL-cholesterol fraction.[9,12] In contrast, a number of studies indicate that wheat bran and other sources rich in water-insoluble fibers do not lower serum cholesterol levels.[11,13] The serum triglyceride effects of high-fiber diets have varied.[8]

Compared with wheat bran's 46% dietary fiber content, oat bran is 30% dietary fiber by weight. Only 8% of the wheat bran fiber is water-soluble, however, while more than 50% of oat-bran fiber is water-soluble. Thus, a gram-equivalent dose of oat bran provides about four times as much water-soluble fiber as wheat bran, and a dietary fiber equivalent dose provides more than six times as much water-soluble fiber.[14]

Using dietary fiber equivalent doses of either oat, wheat, or wheat and oat bran combined, we designed a prospective, randomized, double-blind, controlled study to determine if modest daily doses of oat bran effectively reduce serum cholesterol levels.

Subjects and Methods

Study subjects were volunteers from the first- and second-year medical student classes at the University of California, Irvine, who had completed a three-day record of their prestudy dietary habits. Informed consent was obtained for each subject as specified by the University Human Subjects Review Committee. Subjects were randomly assigned to one of three groups to receive muffins containing one of the following dietary fiber sources: wheat bran and whole wheat flour, oat bran mixed with wheat bran and whole wheat flour, or oat bran alone. These three groups are referred to as "wheat," "wheat/oat," and "oat bran" groups, respectively. Dietary fiber gram-equivalent formulations were achieved using whole wheat flour, wheat bran, and oat bran in a 1:2:3 weight ratio. Muffins were prepared by a licensed professional bakery by adding the different fiber sources to the following basic recipe (relative composition shown by percent of total weight): skim milk (31%), refined wheat flour (8%), brown sugar (16%), vegetable shortening (8%), egg whites (6%), honey (2%), blackstrap molasses (3%), salt and baking soda ($<1\%$), and the respective fiber sources (24%).

Three-day food records submitted by each subject and each muffin recipe (Table 1) used were analyzed for specific nutrients using ESHA Food Processor microcomputer software (ESHA Corporation, Research Nutrition System, Salem, Oregon). Nutrition analysis results were not made available to participants until after the study was completed.

From the Preventive Cardiology Program, Department of Medicine, University of California, Irvine, California College of Medicine. Mr Gold is a medical student at the California College of Medicine, University of California, Irvine.

Supported in part by a National Heart, Lung, and Blood Institute Preventive Cardiology Academic Award HL-01243 to Dr Davidson.

Reprint requests should be addressed to Dennis M. Davidson, MD, C-340 Medical Sciences I Bldg, UCI, Irvine, CA 92717.

ABBREVIATIONS USED IN TEXT

AHA = American Heart Association
HDL = high-density lipoprotein
LDL = low-density lipoprotein

Freshly baked muffins were distributed in opaque plastic bags to the study subjects weekly. The subjects were instructed to eat two muffins a day. They remained unaware of their group assignments throughout the study.

Twelve-hour fasting blood specimens were taken at the beginning and the end of the 28-day muffin ingestion period and were assayed for serum cholesterol, triglyceride, and HDL-cholesterol levels. Cholesterol and triglyceride levels were assayed with the Boehringer Mannheim Diagnostics/Hitachi 704 automated system.[15,16] HDL-cholesterol was assayed using an enzymic heparin-manganese chloride precipitate method.[17,18] LDL-cholesterol was estimated according to the following formula of Friedewald and co-workers[19]:

$$\text{LDL cholesterol} = \text{cholesterol} - \text{HDL cholesterol} - \text{TG}/5$$

where TG is the triglyceride level and TG/5 is an estimate of very-low-density lipoprotein.

Results

Of the original 83 medical students participating in the randomization process, 72 subjects completed the study. Eleven students were excluded for one or more of the following reasons: ingesting fewer than 75% of the formulated bran muffins; pregnancy, serious injury, or illness causing absence and requiring medication during the study (one student each); or having one or more serum specimens rated as "severely hemolyzed" by a laboratory technician not involved in the data analysis (four students). Reasons given for not eating muffins included interference with a dieting regimen (one student), increasing aversion to muffins (two students), and increased bowel frequency (one student). The 11 students not completing the study did not significantly differ from the 72 who completed the protocol in baseline lipid or dietary variables.

The 72 subjects consumed an average of 92% of the muffins provided. Tables 2 and 3 detail the lipid changes noted during the 28-day study period. These include a significant reduction in cholesterol and triglyceride levels in the oat bran group, with no change in HDL-cholesterol levels.

Several baseline variables that could have influenced the above results were analyzed to evaluate the integrity of our randomization process. Table 4 shows the results of this evaluation comparing baseline characteristics of the oat bran group with those in the pooled wheat and wheat/oat groups. No statistically significant differences were noted in baseline age, gender, exercise level, ethanol or dietary cholesterol intake rates, serum cholesterol levels, or in the percentage of muffins eaten. None of the 72 participants smoked cigarettes.

TABLE 1.—*Nutrient Characteristics of Different Muffins Used*

Nutrient	*Wheat*	*Wheat/Oat*	*Oat*
Kcal, per muffin	177.0	188.0	199.0
Total bran, grams	11.3	5.5/8.3	17.0
Dietary fiber, grams*	5.5	5.3	5.0
Total carbohydrate, grams	30.7	30.2	29.7

*One rounded tablespoon of oat bran contains about 5 grams of dietary fiber.

Discussion

De Groot and associates fed human volunteers 140 grams of rolled oats daily in the form of bread for three weeks. This resulted in an 11% reduction in serum cholesterol levels. Replacing the oat bread with normal bread restored mean serum cholesterol levels to 98% of the original levels within two weeks.[20] Several other investigators have subsequently confirmed the hypocholesterolemic properties of oat products (Table 5). A brief synopsis of each study follows.

Using metabolically controlled diets, Judd and Truswell substituted rolled oats for breakfast cereals and wheat flour in ten subjects for three weeks. Plasma cholesterol levels decreased in seven of the ten subjects, but HDL-cholesterol and triglyceride levels were unchanged. Both fecal fat and bile

TABLE 2.—*Group Changes in Serum Lipid Values**

Lipid Type	*A Wheat N=25*	*B Wheat/Oat N=28*	*A+B Pooled N=53*	*C Oat Bran N=19*
Cholesterol	0.0±3.3	0.0±4.0	0.1±2.6†	−9.5±4.3
LDL cholesterol	−2.2±4.0	−1.0±4.0	−1.5±2.8	−9.4±5.3
HDL cholesterol	1.3±1.8	−1.4±1.6	−0.1±1.2	1.3±3.5
Triglycerides	4.6±6.1	12.5±4.6†	8.7±3.8†	−6.3±5.8

HDL=high-density-lipoprotein, LDL=low-density-lipoprotein

*Mean ± standard error of the mean in mg/dl.
†$P<.05$ (one-tailed t test) when compared with the oat bran (C) group.

TABLE 3.—*Summary of Serum Lipid Changes*†*

Serum Lipid Values	*Cholesterol* C	*Cholesterol* A+B	*LDL Cholesterol* C	*LDL Cholesterol* A+B	*Triglycerides* C	*Triglycerides* A+B	*HDL Cholesterol* C	*HDL Cholesterol* A+B
Before	178.8	179.9	108.4	112.0	76.7	73.1	55.0	53.3
After	169.3	180.0	99.0	110.4	70.4	81.8	56.3	53.2
Change	−9.5	+0.1‡	−9.4	−1.5	−6.3	+8.7‡	+1.3	−0.1

HDL=high-density-lipoprotein, LDL=low-density-lipoprotein

*Group mean: mg/dl.
†A=wheat group, B=wheat/oat group, C=oat bran group, A+B=data from both groups pooled
‡$P<.05$ (one-tailed t test) when compared with oat bran (C) group.

acid excretion were significantly increased in subjects on the oatmeal diet, but neutral steroid excretion (including cholesterol) was unchanged. The possible effects of the oat lipid were evaluated by dietary substitution of an oil mixture (corn and nut oils) similar to oat oil for two weeks before and after the oat period. The cholesterol-reducing effects of the oat product were reduced when subjects ingested the oat oil analogue during a control period.[21]

Kirby and co-workers randomly assigned eight men to a biphasic dietary regimen, one phase differing from the other by the inclusion of 100 grams of oat bran. While no changes in the average levels of total cholesterol, LDL cholesterol, or HDL cholesterol occurred during the control (non-oat-bran-ingesting) phase, an overall 13% reduction in cholesterol levels was seen during the oat bran phase, together with a 14% decrease in the levels of LDL cholesterol and no change in the HDL-cholesterol level.[12]

Similarly, Anderson and associates showed this LDL-cholesterol-specific effect using either 100 grams (3.6 ounces) of oat bran or 4 ounces of navy or pinto beans as supplements to the metabolically controlled diets of 20 hyperlipidemic men. The 7-day control and subsequent 21-day experimental diets contained comparable amounts of cholesterol and polyunsaturated and saturated fats. An average 19% reduction in cholesterol levels was seen in both the oat bran and bean diets relative to the preexperimental diet baselines, with 23% and 24% reductions in LDL-cholesterol levels for the two groups, respectively. Improvements in HDL-/LDL-cholesterol ratios of 22% and 17% were evident in both experimental groups despite reductions in HDL-cholesterol levels of 5% and 13% for the oat bran and bean groups, respectively.[9] Long-term lipid profile benefits were noted as subsets of these same subjects continued a similar oat bran-bean diet-augmenting program during the following six months to nearly two years with sustained or actually enhanced overall cholesterol reductions.[23]

TABLE 4.—*Characteristics of Subjects by Study Group*

	*Oat, N=19**	*Others, N=53**
Age, years	26.1± 0.8	25.6± 0.4
Gender, % male (No.)	79 (15)	70 (37)
Exercise†	3.1± 0.2	3.0± 0.1
Ethanol, 0.1 oz/day	1.6± 0.9	1.9± 0.5
Dietary cholesterol, mg/dl	393.5±43.9	334.4±21.9
Prestudy cholesterol, mg/dl	178.8± 7.8	179.9± 4.8
% Muffins ingested	92.6± 1.8	91.6± 1.0

*Average ± standard error of the mean.
†4=maximum, 1=minimum.

In a study similar to the present one, Storch and colleagues used oat bran and wheat bran muffins in a crossover design evaluation of healthy college students with normal baseline cholesterol values. Students received either 50 grams of oat bran or wheat bran in the form of four muffins a day for six weeks, followed by a washout period of seven days. The students then ate the other muffin type for an additional six weeks. Consuming oat bran muffins resulted in a 12% decrease in serum total cholesterol levels, while no significant changes were noted in the wheat bran muffin group.[22]

Van Horn and colleagues studied 208 healthy adult volunteers starting with a six-week washout period during which the participants followed an American Heart Association (AHA) phase I fat-modified diet (total daily fat < 30% total caloric intake, cholesterol < 250 mg per day). Participants then continued the AHA diet for an additional six weeks, isocalorically supplanting their carbohydrate intake with either 60 grams per day of oat bran (group 1), 60 grams per day of oatmeal (group 2), or no addition to the phase I AHA diet (group 3). Oat product ingestion was 39 and 35 grams per person per day for groups 1 and 2, respectively. Intake of other fiber sources was not significantly changed during the study period. Subjects in all three groups experienced a 5.2% reduction in cholesterol levels during the six weeks of the AHA diet alone. Groups 1 and 2 had further cholesterol reductions of 2.7% and 3.3%, respectively, during the second six weeks; no change in serum cholesterol levels was seen in control group 3 during this time. The reduction in cholesterol values of combined groups 1 and 2 was statistically significant when compared with that of the control group 3.[24]

When the results of the present study are included with

TABLE 5.—*Human Studies Evaluating Oat Product Lipid Effects*

Study and Grain(s)	*Subjects, No.*	*Dose, Grams/Day*	*Days on Diet, No.*	*Prestudy Cholesterol Level, mg/dl*	*Change in Cholesterol, %*
De Groot et al, 1963[20]					
Rolled oats	21	140	21	251	−11
Judd and Truswell, 1981[21]					
Rolled oats	10	125	21	203	− 8
Kirby et al, 1981[12]					
Oat bran	8	94	10	269	−13
Anderson et al, 1984[9]					
Oat bran	10	100	21	257	−19
Storch et al, 1984[22]					
Oat bran	12	50	42	185	−12
Chen and Anderson, 1986[23]					
Oat bran/beans	10	41/145	182	257	−26
Oat bran/beans	4	41/145	693	257	−22
Van Horn et al, 1986[24]					
Oat bran	69	39	28	196	− 3
Rolled oats	69	35	28	195	− 3
This report					
Oat bran	19	17	28	179	− 5

those of the oat bran studies described above,[9,12,22,24] the oat bran dose used correlates well with the percent decrease in cholesterol values ($r = .867$). This relation can be roughly approximated by % decrease in cholesterol = 0.156 × (gram oat bran/day) + 1.0.

As more data become available, it may be feasible in the future to use similar formulations to estimate cholesterol responses for a given prescription dose of an oat product.

The findings of the studies mentioned involving serum lipid subfraction analysis suggest that the hypocholesterolemic effects of oat products selectively involve reducing the LDL fraction while generally not affecting the HDL-cholesterol subfraction. These results are encouraging considering that the significant side effects seen with most currently available pharmacologic hypocholesterolemic agents are not mentioned in association with ingesting oat products in the studies reviewed here.[25]

Though the specific cholesterol-reducing mechanisms of oat bran are still being clarified,[24] evidence that it may be useful as a therapeutic adjunct is increasing. The advantages of using oat products include low cost and availability. Other benefits noted in an elderly population using oat bran meal biscuits included relief from constipation—with respect to bowel frequency, stool type, and associated pain—and a significant average weight loss.[26]

From the present study, we conclude that daily ingesting of 17 grams (two rounded tablespoons) of oat bran can significantly reduce serum total cholesterol and serum triglyceride levels in a young, healthy population. The serum cholesterol reduction appears to primarily involve the LDL subfraction. These findings reinforce those reported by others, and though the long-range health consequences of increased dietary oat product use have yet to be shown, there is mounting evidence that such dietary augmentation results in an improved, cardioprotective lipid profile.

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Piroxicam and Doxepin—An Alternative to Narcotic Analgesics in Managing Advanced Cancer Pain

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To provide an effective continuum of the relief of severe carcinomatous pain with minimal side reactions, we initiated treatment with piroxicam (60 to 120 mg per day) and doxepin hydrochloride (25 to 225 mg per day). Of 30 patients presenting with severe pain of cancer of various origins, 7 continued to death with piroxicam and doxepin therapy. An additional 17 were successfully treated for 6 to 66 weeks with therapy reported here but, as disease progressed, required supplemental narcotics. The remaining six abandoned the use of piroxicam due to complications of therapy, which ranged from diarrhea to gastric perforation; serious complications were associated with patients' failure to adhere to a prescribed regimen of sucralfate. Therapy with piroxicam and doxepin proved to be safe and efficacious.

(Cohn ML, Machado AF, Bier R, et al: Piroxicam and doxepin—An alternative to narcotic analgesics in managing advanced cancer pain. West J Med 1988 Mar; 148:303-306)

Severe pain in patients terminally ill with cancer is managed in many countries, including the United States, almost exclusively with narcotic analgesics.[1] The justification for using these compounds relies on the belief that no other category of analgesic drug is potent enough to assuage the incapacitating pain frequently experienced by patients in advanced stages of cancer. Nonetheless, it has been reported in the United States and Great Britain that about 25% of patients with terminal cancer syndromes endure pain that is inadequately controlled,[2] and cancer pain is generally considered among the most critical of health issues facing many countries.[3] The failure to provide adequate relief stems primarily from the fact that the elevated doses of narcotics required to palliate severe carcinomatous pain commonly produce such adverse effects as anxiety, depression, confusion, insomnia, anorexia, and constipation, which greatly compound both physical discomfort and the fear of death and dying common, in varying degrees, to all patients terminally ill with cancer. In the effort to counteract the narcotic-induced side effects or enhance the alleviation of pain, or both, such widely various compounds as tranquilizers, antidepressants, hypnotics, phenothiazines, and marijuana have been proposed. Unfortunately, these drugs often intensify existing adverse effects or induce additional side reactions without significantly augmenting pain relief.

In the present investigation, we report that treatment with a nonnarcotic drug regimen consisting of the long-acting, nonsteroidal anti-inflammatory drug (NSAID) piroxicam, in combination with the tricyclic antidepressant doxepin hydrochloride, provides effective pain relief and an increased sense of overall well-being to patients referred for the management of severe pain associated with advanced stages of cancer.

Patients and Methods

The 30 patients in this study were referred to the Pain Management Center with terminal cancer syndromes and after receiving specific tumor therapies including surgical treatment, chemotherapy, and radiotherapy. Patients' ages varied from 34 to 86 years but were definitely skewed toward the fourth and fifth decades; the treatment group consisted of 14 men and 16 women, all of whom presented with malignant, histologically well-defined tumors of various causes. There was no single, predominant tumor type, but lung, colon, and breast were the most frequently represented (Table 1). Associated in each case with the advanced cancer syndrome was severe, unrelenting pain. For pain control, this patient population had been prescribed liberal doses of a minor narcotic analgesic (codeine or oxycodone) in combination with aspirin or acetaminophen. Despite extensive use of these compounds, however, all patients experienced inadequate pain control; thus, many had also been prescribed a wide variety of psychotropic drugs. As this group of patients commonly exceeded prescribed analgesic doses due to poor pain control, it was not possible to accurately record narcotic usage before this study. Patients being treated with major narcotic analgesics at the time of referral were excluded from the present trial.

At the start of investigation, a thorough medical evaluation, including a detailed history, comprehensive physical examination, complete blood chemical assessment, and review of previous medical history, radiographic films, and pathology reports, was conducted for each potential participant in an attempt to determine the origin and cause of pain and to exclude patients presenting with hemorrhagic diatheses, hematologic deficiencies, hepatic or renal failure, or a history of gastrointestinal bleeding or peptic ulcer.

Before the signing of informed consent, each patient was fully informed regarding the possibility of adverse effects associated with piroxicam and doxepin administration. Patients were encouraged to continue using narcotic analgesics if pain was inadequately controlled by the nonnarcotic therapy but were asked to carefully record dosages and sched-

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ules of administration. Participants were further assured that major narcotics would be made available if required.

Therapy began with a regimen of 60 mg of piroxicam per day taken in the evening 15 minutes after taking 1 gram of sucralfate. The dose of piroxicam was increased weekly by 20 mg until the patient reported being pain-free or until a maximum daily dose of 120 mg was reached. Concurrently, doxepin was prescribed to be taken on a daily basis (two to three hours before bedtime); all other psychotropic therapy was discontinued. In consultation with the Pain Management Center medical staff, patients were allowed to titrate their own daily doses of doxepin between 25 and 225 mg (mean 92.5 mg, refer to Table 1) in weekly increments of 25 mg; they were advised that the optimal dose was one that would permit sleeping through the night without causing drowsiness during the day. All drugs were administered orally.

Twice-a-week visits for medical and supportive care allowed the medical staff to adjust dosages of medication and obtain information pertaining to narcotic usage, breakthrough pain, therapeutic efficacy, and psychological state. At each visit, patients underwent laboratory tests, including a complete blood count, electrolytes, hepatic enzymes, liver and renal function, and examination of a stool specimen for occult blood. These terminally ill patients were concomitantly receiving psychiatric supportive care and, if needed, social services. Additionally, the Pain Management Center medical staff was available by telephone at all times.

Results

The causes of our patients' pain syndromes were as diverse as their tumor types (Table 1). The average survival time was 6.17 months and ranged from 2 to 16.5 months. Of the 30 patients, 7 continued to death with piroxicam and doxepin therapy; these patients required narcotics only occasionally for breakthrough pain. An additional 17 continued the therapy reported here but, as the disease progressed, required supplemental narcotics on a daily basis. The remaining six abandoned the use of piroxicam due to complications of therapy.

Patients whose pain was adequately controlled with piroxicam and doxepin uniformly reported an increased sense of overall well-being despite progression of the disease. This group of patients showed increasingly positive interactions with family, friends, and medical staff, and most gained weight. Disregarding information provided by the medical staff, five of these patients interpreted freedom from pain as remission of their disease and stopped taking their medication. Though there was no immediate reaction to this cessation, within 48 to 72 hours, pain returned with its initial intensity. As restarting the regimen of piroxicam and doxepin proved ineffective for the first day or two, these patients visited the clinic reporting that they had again begun taking narcotic analgesics because the medication "wasn't working." Only after careful questioning did we discover

TABLE 1.—*30 Patients Treated for Severe Carcinomatous Pain With a Regimen of Piroxicam and Doxepin Hydrochloride*

Patient No.	Sex	Age, yr	Site of Primary Cancer	Dose of Piroxicam, mg/day	Dose of Doxepin, mg/day	Duration of Pain Relief Without Narcotic Supplementation, wk	Complications of Therapy
1	♀	50	Lung	80	50	12	Dyspepsia
2	♀	47	Lung	80	25	11	...
3	♀	51	Cervix	100	50	16*	...
4	♀	44	Lung	100	50	20	...
5	♂	49	Colon/bladder	100	125	17	...
6	♀	50	Skin	120	150	25*	...
7	♀	48	Larynx	80	125	19	Gastrointestinal bleeding
8	♂	63	Tonsil	80	50	9*	...
9	♂	53	Colon	120	125	15*	...
10	♂	48	Nasopharynx	80	100	22*	...
11	♂	67	Multiple myeloma	60	50	47	Dizziness
12	♂	45	Lung	120	100	16	...
13	♂	47	Kidney	80	50	52	Gastric perforation
14	♂	65	Prostate	80	125	19	...
15	♂	56	Pancreas	80	100	15	...
16	♂	56	Lung	100	100	41	Gastrointestinal bleeding
17	♂	58	Tonsil	80	225	8	...
18	♀	44	Lung	80	50	21	...
19	♂	52	Lung	80	150	31	...
20	♂	51	Rectum	120	150	51	...
21	♀	86	Uterus	60	25	8*	...
22	♀	52	Lung	100	50	28	Dyspepsia
23	♀	51	Lung	60	150	16	Dyspepsia
24	♀	42	Breast	80	150	6	...
25	♀	45	Bone	80	100	66	Tinnitus
26	♀	65	Breast	80	100	7	...
27	♀	34	Cervix	100	75	12	Dyspepsia
28	♂	55	Lung	100	75	16	...
29	♀	40	Breast	80	50	13*	...
30	♀	42	Breast	60	50	5	Diarrhea

*Denotes patients who continued piroxicam and doxepin therapy without narcotics until death.

what had occurred; for these patients, piroxicam and doxepin therapy was successfully resumed.

The major side reaction due to elevated doses of piroxicam was gastrointestinal toxicity. Of the patients who consistently took sucralfate before piroxicam, none had bleeding or ulcer formation; four, however, complained of dyspepsia, an adverse effect that was alleviated when the sucralfate dosage was increased to 2 grams per day. Central nervous system side effects, such as dizziness and tinnitus, caused two of our patients to withdraw from the clinical trial; their symptoms cleared after piroxicam therapy was discontinued. We observed no cases of agranulocytosis or aplastic anemia. One patient presented with a blood platelet depression that remained unchanged when the piroxicam therapy was stopped for two weeks and restarted. Renal function and serum electrolyte values remained normal even in one patient who had undergone a nephrectomy due to adenocarcinoma. In patients who exhibited alterations in liver function, liver scans showed direct tumor involvement; no cases of hepatic dysfunction proved attributable to piroxicam and doxepin therapy. None of the patients displayed dermatologic, allergic, or ophthalmologic reactions to piroxicam.

The longest period of survival was 16.5 months. In this patient, as in all others, there was no development of tolerance or escalation of the dose of either piroxicam or doxepin. A thorough review of the cases of all patients indicated that cancer was the cause of death; in no case was there evidence suggesting a contributory effect of piroxicam and doxepin therapy.

Discussion

Once therapeutic procedures intended to control tumors have been exhausted, it is generally agreed upon that pain control is a principal objective in the treatment of patients presenting with advanced forms of cancer. Narcotic analgesics have been the primary compounds used in the pharmacologic attempt to alleviate severe carcinomatous pain.[1] Because alternate drug therapies are, in general, considered inadequately effective, opiate analgesics have been used despite their patently negative impact on patients' well-being. Although for this preliminary investigation we were unable to "objectively" measure the quality of life, our patients without exception reported an increased sense of overall well-being and, in most cases, excellent pain palliation. Thus, what have been termed "key" components[4] of increasing the quality of life in terminally ill patients—preventing or alleviating physical and psychological stress, maintaining physical and mental functioning, and controlling pain—have been fulfilled to the best of our estimation.

Some of the improved sense of well-being uniformly reported by these patients suffering from severe pain associated with advanced stages of cancer was undoubtedly due to the therapeutic inclusion of the tricyclic antidepressant, doxepin. Even small doses of doxepin effectively palliated symptoms such as insomnia, fatigue, and depression. In addition, there is general agreement[5-7] that the use of tricyclic antidepressants in managing pain does not require elevated doses; nonetheless, the question of whether these compounds directly affect pain perception remains controversial.[8]

Compared with narcotic analgesics, the primary advantages of therapy with piroxicam and doxepin are that these compounds are neither addictive nor associated with tolerance, respiratory depression, psychotropic disturbances, central nervous system depression, or anorexia. Piroxicam was selected as the NSAID in this investigation due to its long plasma half-life,[9] which allowed the administration of this compound once per day with effectiveness. This is an important factor as, in our observation, failure to obtain a continuum of pain control with shorter acting NSAIDs is a major rationale for discontinuing NSAID therapies. In addition, a single daily administration of medications is far more conducive to patients' compliance than a regimen requiring the administration of one or more analgesics several times per day.[9]

Past experience (unpublished observations) indicated 60 mg per day as the appropriate starting dose for piroxicam; most patients with pain from advanced forms of cancer, however, required 80 mg per day and some as high as 120 mg per day (Table 1). Patients uniformly reported an analgesic effect 48 to 72 hours subsequent to the initiation of therapy; this lag period is characteristic of piroxicam.[9] In agreement with reports that, despite its long plasma half-life, piroxicam's low drug burden prevents accumulation of this compound,[9,10] no cumulative effects of piroxicam were observed in this trial, and frequent laboratory tests and thorough medical reviews of all patients greatly reduced the degree of risk. Three of our patients took it upon themselves to divide the dose of piroxicam in the manner they were accustomed to taking other NSAIDs. These patients, as they lacked sufficient sucralfate for multiple administrations of piroxicam, had the rapid development of signs of gastrointestinal distress. Within two weeks, two of these patients suffered gastrointestinal hemorrhaging and had to discontinue therapy. A fourth patient who failed to take sucralfate before piroxicam required surgical repair of a silent perforation of a gastric ulcer.

All current modalities of analgesic drug therapy require the striking of a judicious balance between pain relief effectiveness and toxic side effects. All NSAIDs are associated with a potential for gastrointestinal ulceration, perforation, and bleeding; one responsible mechanism is the inhibitory effect NSAIDs exert on prostaglandin synthesis.[11] Specifically, NSAIDs, including piroxicam, inhibit arachidonic acid from converting to prostaglandin endoperoxide, thus reducing cytoprotection of the upper gastrointestinal tract. The toxic actions of piroxicam on various systems have been comprehensively reported.[12,13]

At the start of this clinical trial, the Pain Management Center medical staff was aware that an inability to prevent gastrointestinal toxicity would lead to the failure of piroxicam and doxepin therapy. The well-known anticholinergic effect of doxepin has been shown to reduce gastrointestinal stress by decreasing total gastric acid secretion,[14] but this effect alone does not provide full protection. In previous trials with this therapy, we prescribed cimetidine to prevent gastrointestinal upset; in our experience, however, this drug proved inadequately protective, an observation that correlates with subsequently published reports that cimetidine is ineffective in cases of nonulcer dyspepsia.[15] Thus, we prescribed sucralfate, which prevented peptic toxicity except in the four cases previously referred to wherein the patients admitted to disregarding our instructions concerning its use. The effectiveness of this compound in averting gastrointestinal complications is in agreement with reports that sucralfate provides both short-term and long-term protection to patients on a continued regimen of NSAIDs.[16] The recently introduced prostaglandin

endoperoxide analogue, misoprostol, may serve even better in preventing gastrointestinal toxicity.

It is interesting to note that NSAIDs are not as "mild" analgesics as they are often termed. In comparing the efficaciousness of aspirin and morphine for postsurgical pain, the two compounds were found to provide equally effective relief.[17] Moreover, NSAIDs have been reported to control severe pain "in many situations," including cases of pain associated with cancer.[18] The daily dosage of piroxicam required by our group of patients was as much as six times the suggested dose of 20 mg a day; the suggested dose, however, is based on anti-inflammatory activity using arthritic models.[19-22] In our observation, the control of severe pain of a malignant origin requires a minimum of 40 mg per day and, more commonly, 60 to 100 mg per day. Establishing effective analgesic activity requires two to four days, a latency of onset that may be attributed to extensive serum protein binding[9]; consequently, piroxicam should always be administered on a scheduled basis, never only as needed. Dosages should be gradually increased until the desired level of analgesia is reached or until adverse side reactions develop. Our observations indicate that, for most patients, 120 mg per day is the maximum dose that may be safely tolerated in combination with doxepin and an adequate course of sucralfate.

While mild hepatic dysfunction and, in rare cases, severe hepatitis have been associated with administering piroxicam,[16] we observed no hepatitis, cholangitic jaundice, or alterations in hepatic enzymes. As renal activity plays a limited role in the metabolic elimination of piroxicam,[23] renal toxicity due to this compound is rarely reported in patients with normal kidney function,[24] and, in the present trial, piroxicam administration resulted in no nephrotoxicity. Because of its inhibitory effect on prostaglandin synthesis, piroxicam may cause fluid retention and decreased sodium excretion.[10] Although no such effect occurred in the patients in this study, careful evaluation is indicated.

Because NSAIDs suppress fever, disease states characterized by a febrile reaction may go undetected in patients taking piroxicam on a long-term basis. Again, this clinical observation serves to stress the importance of systematic follow-up for patients on a piroxicam and doxepin regimen. All NSAIDs exhibit, as well, the potential to interfere with platelet function or cause agranulocytosis or aplastic anemias. Although blood dyscrasias were noticeably absent in the present group of patients, we may expect, in a larger sampling of subjects, such toxic effects to occur. For that reason and the fact that difficulties may arise in distinguishing between adverse effects elicited by piroxicam and symptoms due to progressing cancer syndromes, patients prescribed piroxicam and doxepin therapy for severe carcinomatous pain should be observed with extreme caution, and, of course, piroxicam should not be administered concomitantly with chemotherapy. Frequent blood and stool assessments are a necessary safeguard against occult toxicity.

In assessing the applicability of piroxicam and doxepin therapy, we note that effective pain relief was achieved despite the diversity of tumor types, resulting in widely various pain origins in this patient population; it is also interesting that the therapy proved equally effective for pain arising from visceral and bony sources. In accordance with the World Health Organization's guidelines for the management of carcinomatous pain, patients should be treated with nonnarcotic analgesics for as long as effective pain relief may be maintained with relative safety. It has been reported, however, that in most patients the time period of management with narcotics is "more than twice as long" as that of nonnarcotic management, which is generally "less than three weeks."[25] The present study would seem to indicate the possibility of reversing that time frame in many patients.

Overall, piroxicam and doxepin therapy for extreme pain due to various terminal cancer syndromes has proved, in this limited trial, to be an efficacious and beneficial alternative to management with narcotic analgesics regardless of the severity, duration, or origin of pain. The therapy may prove particularly useful in patients who do not respond well to narcotic analgesics.

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Prevalence of Hepatitis δ (Delta) Virus Infection
A Seroepidemiologic Study

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In assessing the prevalence of hepatitis δ (delta) virus (HDV) infection in 358 patients with acute hepatitis B seen in Los Angeles between 1983 and 1985 and in 196 patients with chronic hepatitis B followed between 1980 and 1985, we found that 23% of patients with chronic and 5% of patients with acute hepatitis B were infected with HDV. Among patients with chronic hepatitis B, the prevalence of HDV infection was 73% in intravenous drug users and 14% in homosexual men. Acute coinfection with the hepatitis B virus was also more frequent in drug users (8%) than in other groups. δ-Hepatitis is a common infection in hepatitis B virus carriers in Los Angeles, particularly in drug addicts, but also in homosexual men who do not abuse drugs intravenously.

(DeCock KM, Jones B, Govindarajan S, et al: Prevalence of hepatitis δ (delta) virus infection—A seroepidemiologic study. West J Med 1988 Mar; 148:307-309)

Infection with the hepatitis δ (delta) virus (HDV) is restricted to persons also infected with the hepatitis B virus (HBV), either as acute coinfection with HBV, or as acute superinfection in HBV carriers, or as a chronic infection with both viruses.[1] The importance of this recently recognized agent stems from its frequent association with severe hepatitis following acute infection[2-4] and with serious progressive liver disease in patients with chronic HDV infection.[5,6]

Despite a reasonable understanding of the clinical expression of HDV infection and its diagnosis, knowledge concerning its epidemiology is limited. The current opinion is that δ-hepatitis in the United States is largely restricted to intravenous drug users, although a high rate of infection has also been reported in persons with hemophilia.[7] It has been considered rare in other groups at risk for HBV infection.

We present here the results of a seroepidemiologic study to assess the prevalence of HDV infection in patients from different risk groups with acute and chronic hepatitis B in Los Angeles. The results show high rates of HDV infection in drug users and in homosexual HBV carriers and indicate a need for similar studies in other parts of this country.

Patients, Materials, and Methods

Patient Selection

Patients were drawn from the free-of-charge hepatitis clinic that is held weekly at the Los Angeles County-University of Southern California Medical Center. This hospital is the largest medical facility in Los Angeles and serves primarily the indigent population of the city.

To assess the prevalence of HDV infection, 358 patients with acute hepatitis B and 196 patients with chronic hepatitis B were tested for the presence of the δ-agent antibody. These unselected cases represent all the patients with acute HBV infection seen in this clinic between May 1983 and May 1985, and of cases of chronic HBV infection followed for more than six months between January 1980 and November 1985, that met the case definition outlined below.

Patients were considered to be suffering from acute HBV infection when they presented with acute icteric hepatitis, were positive for the hepatitis B surface antigen (HBsAg), and had elevated aminotransferase levels to at least ten times the upper limit of normal. All those found to be positive for the δ-antibody were tested for immunoglobulin (Ig) M antibody to the hepatitis B core antigen (anti-HBc) to distinguish any cases of acute HDV superinfection of the chronic HBV carrier state. Patients with chronic HBV infection were documented HBsAg-positive for at least six months. Patients were allocated to epidemiologic groups according to the history given concerning risk factors for hepatitis.

Testing for the HDV antibody became available to us on a routine basis in early 1983. HBsAg-positive patients seen from then on were mostly tested prospectively, at one of their initial attendances at the clinic. Patients seen before 1983, and a few seen later who had escaped testing, had anti-HDV tests done on stored serum.

Serologic Tests

HBsAg was detected by commercially available radioimmunoassay kits (Abbott Laboratories, North Chicago, Ill). IgG and IgM antibody to HDV was detected by solid-phase-capture radioimmunoassay, as previously described.[3,8] Using this technique, results are expressed as the number of counts per minute of the test serum to the counts per minute of a negative control, positive being greater than 2.1 ratio units. Either antibody is indicative of HDV infection; the pattern of δ-antibodies in different categories of infection has been previously described.[9] Anti-HBc IgM was measured on column-separated IgM using a commercially available radioimmunoassay for the anti-HBc (Abbott Laboratories).[10]

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Reprint are not available.

ABBREVIATIONS USED IN TEXT

anti-HBc = antibody to hepatitis B core antigen
HBsAg = hepatitis B surface antigen
HBV = hepatitis B virus
HDV = hepatitis δ (delta) virus
HIV = human immunodeficiency virus
Ig = immunoglobulin

Statistical Analysis of Results

Data were analyzed using the χ^2 test on results set out in two-by-two contingency tables.

Results

The prevalence of the δ-agent antibody in patients with acute and chronic HBV infection is shown in Table 1. Chronic hepatitis B was complicated by HDV infection in 23% of all cases, compared with 5% of cases of acute HBV infection ($P<.001$). Infection with HDV was noted in 73% of intravenous drug users with chronic HBV infection, compared with 14% of non-drug-using homosexual men ($P<.001$). Total numbers in the other groups with chronic HBV infection were considered too small for comparison; HDV infection rates in these patients were low. Of 27 Asian patients with chronic hepatitis B, the only one with anti-δ antibody was a young man with persistent generalized lymphadenopathy, a low helper/suppressor T-cell ratio, and antibody to the human immunodeficiency virus (HIV). He said he was not homosexual and did not abuse drugs intravenously.

In patients with acute hepatitis B, coinfection with HDV was more prevalent in intravenous drug users (8%) than in all other patients (3%) ($P<.02$).

TABLE 1.—*Prevalence of Hepatitis δ (Delta) Virus Infection*

Risk Group	Acute Hepatitis B δ-Positive No.	Acute Hepatitis B δ-Positive %	Chronic Hepatitis B δ-Positive No.	Chronic Hepatitis B δ-Positive %
Intravenous drug user	12/160	8	27/37	73
Male homosexual	1/67	1	14/98	14
No risk factor evident	4/131	3	2/24	8
Asian	...	...	1/27	4
Health care worker	...	...	1/4	25
Transfusion	...	...	0/2	0
No information	...	...	0/4	0
Total	17/358	5	45/196	23

Discussion

Factors that have hampered understanding of the epidemiology of HDV infection include the restricted availability of test systems, the selected nature of patient groups examined, the short duration of antibody expression following healed infection, and the clinical similarity between HBV and HDV infections. There is a need for clinical and seroepidemiologic studies to determine the importance of HDV infection as a cause of acute and chronic liver disease worldwide.

In an earlier clinical study of δ-hepatitis,[9] we showed that two thirds of our cases were associated with chronic HBV infection. The results of the present study, incorporating denominator population data and based on unselected outpatients, provide meaningful prevalence figures. While inevitable bias exists in hospital-based studies, many of our patients with chronic HBV infection attend for follow-up despite an absence of symptoms or for specific treatment, and significant weighting to more serious chronic liver disease in this study is unlikely.

HBV carriers are particularly likely to be infected with HDV, and these patients bear the burden of this infection. With 23% of all our HBV carriers and 5% of our patients with acute HBV infection affected, it is evident that δ-hepatitis is not a rare condition in this part of the United States.

TABLE 2.—*Reported Prevalence of Hepatitis δ (Delta) Virus Infection in United States HBsAg Carriers*

Source	Risk Group and State*	δ-Agent Prevalence, %
Rizzetto et al, 1979[11]	Chronic liver disease, New York	21
	Chronic liver disease, New Jersey	41
	Symptomless carriers, New Jersey	6
Rizzetto et al, 1980[12]	HBsAg carriers, Maryland	0
	HBsAg carriers, New Jersey	23
	HBsAg carriers, California	33
	Polytransfused hemophiliacs, Maryland	45
Ponzetto et al, 1984[13]	Intravenous drug users, Washington, DC, Miami, New Jersey	42
Nath et al, 1984[14]	Asymptomatic blood donors	4
Mushahwar and Decker, 1984[15]	Carriers, California	2
	Commercial donors, California	7
	Volunteer donors, Florida	4
	Volunteer donors, Hawaii	7
	Homosexual men, Illinois	0
	Volunteer donors, Kansas	2
	Drug addicts, Texas	52
	Volunteer donors, Texas	8
Jacobson et al, 1985[16]	Drug addicts, New England	41
	Homosexual men, New England	4
Shiels et al, 1985[17]	Homosexual men, Minnesota	18
	Drug addicts, Minnesota	19

HBsAg = hepatitis B surface antigen

*Risk group is as defined in the source quoted.

Table 2 summarizes data concerning the prevalence of HDV infection in patients with chronic hepatitis B reported from elsewhere in this country. Prevalence rates in Los Angeles are among the highest reported from anywhere else in the United States or northwestern Europe.

Our data show a clear association between parenteral inoculation and infection with the δ-agent. Intravenous drug users, irrespective of whether they had acute or chronic HBV infection, suffered HDV infection significantly more frequently than other groups at risk. Presumably, direct percutaneous injection is the most efficient way to transmit the agent and establish δ-infection.

We have previously reported a substantial proportion of homosexual men among our patients who have δ-hepatitis.[9,18] The 14% prevalence of HDV infection among homosexual HBV carriers documented here shows that in Los Angeles, significant transmission of HDV occurs within the homosexual community. A prevalence of 18% HDV infection in homosexual HBV carriers was reported from Minnesota,[17] but numbers were small in that study and patients highly selected.

Other groups have reported high rates of HDV infection in persons with hemophilia,[7] and infection has been documented occasionally in patients receiving dialysis[19] and in residents of institutions for the mentally subnormal.[20] The nature of our clinic prevented us from assessing these groups at risk.

The pronounced association between HDV and chronic, rather than acute, HBV infection in all risk groups reflects the ease with which infection with the δ-agent can be established and maintained in this situation. Experimentally induced infections in chimpanzees have shown that a lower dose of HDV is required to initiate infection in patients with chronic hepatitis B than in the case of coinfection with acute hepatitis B.[21(p79)] In addition, coinfection is a restricted situation requiring exposure to appropriate quantities of both agents, whereas chronic HBV infection offers a continuous environment promoting rescue of the defective superinfecting agent. These factors probably explain the frequency of HDV superinfection compared with coinfection and may be particularly important in the case of relatively inefficient modes of transmission such as sexual activity.

Although the number in the present study was small, HDV infection was rare in other groups with HBV infection, apart from homosexual men and drug users. Only 1 Asian patient was found to be infected, in keeping with other reports of a low HDV prevalence in the Far East.[22]

In conclusion, this study of HDV prevalence, less selective than others cited in Table 2, has documented a high rate of infection in Los Angeles. Carriers of the hepatitis B virus are particularly at risk, and although drug users are the main group affected, HDV infection in this city is also prevalent in homosexual men. These findings have serious implications because our own experience[6,8] and that of others[5] indicate a high frequency of advanced liver disease in patients with chronic HDV infection.

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Sternoclavicular Bacterial Arthritis

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Bacterial infection of the sternoclavicular joint is an unusual event, with cases being reported in those with diabetes mellitus, in intravenous drug abusers, and in patients afflicted with rheumatoid arthritis. A case of this unique infection occurred in a person not known to be at risk for septic arthritis. Our report shows the difficulty in diagnosing this disorder.

(Mozen PH, Zell SC: Sternoclavicular bacterial arthritis. West J Med 1988 Mar; 148:310-312)

Septic arthritis is a relatively uncommon occurrence. In a large, hospital-based study from 1958 to 1967, Kelly reported only 78 cases occurring in the nine years.[1] Others have confirmed the relative infrequency of this infection in subsequent series.[2,3] Although the knee and hip are the most commonly involved joints, bacterial infection limited to involvement of the sternoclavicular joint does occur, but rarely,[2-5] with most reports being described in intravenous drug abusers[6-8] and among patients afflicted with rheumatoid arthritis.[1,9-13] Some authors even claim rheumatoid patients to have a predilection to sternoclavicular joint infection, suggesting an increased risk in the absence of intra-articular or systemic steroid therapy.[10,13,14]

Sternoclavicular septic arthritis is rare in healthy patients. In an extensive literature review, we found only one case of documented sternoclavicular septic arthritis reported in a previously healthy patient in association with a tooth extraction.[15] Five other cases of this infection have been reported in persons with diabetes mellitus[4-5,16]; evidence suggests, however, that a decreased phagocytic response may predispose to bacterial infections in such patients.[17]

We report a case of documented infection of the sternoclavicular joint occurring in a patient not known to be at risk for septic arthritis. This case shows the difficulty of making the diagnosis of sternoclavicular joint infection and the consequences of delayed treatment in this life-threatening infection. A physician must maintain a high index of suspicion in any patient presenting with swelling and tenderness around the sternoclavicular joint associated with fever and signs of septic shock.

Report of a Case

The patient, a 61-year-old active and robust man, was seen in the outpatient clinic because of a two-day history of left shoulder pain, fever, and generalized lethargy. A chest x-ray film showed a patchy infiltrate in the region of the left upper lobe (Figure 1). The patient was given ampicillin for presumed pneumonia and told to return if symptoms did not improve. He returned two days later with increasing fever and episodic, shaking chills. His medical history was remarkable only for hypertension that was well controlled. He also had mitral valve prolapse diagnosed by echocardiogram in the past but was asymptomatic.

The patient was admitted to the hospital for evaluation of his left upper lobe mass and a regimen of cefazolin and gentamicin sulfate started for the treatment of pneumonia. A bronchoscopy done on the day following admission was normal. On the second day of admission the patient decompensated, with hypotension and respiratory failure developing, requiring intubation. Large volumes of fluid and the intravenous administration of pressor agents were required to maintain the blood pressure. The cardiac output was 11.7 liters per minute, systemic vascular resistance was 260 dynes per sec per cm^{-5}, and the calculated oxygen extraction was 15%, all consistent with septic shock. At this time, bilateral swelling of the neck and facial plethora developed, suggesting superior vena caval obstruction. Chest films revealed an extensive left pleural effusion with opacification of the left hemithorax. A computed tomographic (CT) scan of the chest showed a large amount of fluid extending posteriorly along the entire left lung with compression of the left lower lobe. At this time blood cultures grew *Staphylococcus aureus* in three out of four bottles. The antibiotic therapy was changed to nafcillin sodium and cefotaxime sodium. A surgeon was consulted, and a chest tube was inserted to drain a suspected empyema. Two liters of light tan, clear fluid consistent with a transudate were drained; cultures were negative.

On day 4 the patient was weaned off pressors, the endotracheal tube removed and his condition stabilized, but he had a persistent low-grade fever. Feeling that a source of infection was still present, a CT scan of the neck was recommended by an ear, nose, and throat specialist and showed soft tissue swelling with the loss of tissue planes in the region of the left sternoclavicular joint (Figure 2). A bone scan was also abnormal in the region of the left sternoclavicular joint and the first rib.

A presumptive diagnosis of sternoclavicular joint infection was made, and it was thought necessary to take the patient to surgery. Purulent material was found leaking from the left sternoclavicular joint with contiguous spread to the left anterior chest wall. The anterior mediastinum was also explored and found to contain necrotic material and pus. Cultures were taken, the wound was irrigated, and a drain was left in the mediastinum. All cultures grew *S aureus.* The patient made an excellent recovery, became afebrile, and his leukocyte count gradually decreased to normal coincident with a slow clearing of the infiltrate in the area of the left upper lobe.

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Discussion

In general, most cases of septic arthritis present with joint pain and swelling, with fever being variable and occurring in 30% to 60% of patients.[1] On the contrary, sternoclavicular septic arthritis, an uncommon infection, has no typical presentation. Often the progression of infection is insidious, delaying a diagnosis until anterior chest pain, shoulder discomfort, joint swelling, and fever become the primary complaints, as shown by the case reported herein.[6,8] Infection of the sternoclavicular joint, however, can also present acutely with high fever, bacteremia, and septic shock dominating the clinical complex.[5] Perhaps the anatomic proximity of the sternoclavicular joint to the great vessels facilitates rapid bacteremia, leading to septic shock and obtundation before signs and symptoms of joint infection become clinically apparent.

Although joint fluid aspiration with a positive identification of a pathogen is the mainstay of a diagnosis of septic arthritis, successfully obtaining fluid from the sternoclavicular joint is technically difficult and nondiagnostic in most cases.[18] As a result, relying on noninvasive techniques to make the diagnosis becomes necessary but has technical limitations. Plain roentgenograms of the chest are insensitive for detecting bony changes in the sternoclavicular joint for several reasons. First, they are difficult to visualize in the anteroposterior projection because of overlapping bones and soft tissue densities. In addition, radiographic changes suggesting osteomyelitis are a late finding and are not initially present in most cases.[2,5] Standard tomography is often not helpful as it is time-consuming and costly.[19] Computed tomography has been advocated as a superior method for providing an anatomic image of the sternoclavicular joint area.[19] It provides a much sharper image of the soft tissues and fascial planes and clear images of the bones and joints so that even small erosions can be seen.[19] This is shown in our case, in which a CT scan was instrumental in suggesting the diagnosis, and an aggressive surgical approach facilitated documenting and identifying the infection.

Figure 1.—A chest film done two days before admission shows a left upper lobe infiltrate.

Several unexpected findings associated with sternoclavicular joint infection deserve mention. Our patient had suppurative mediastinitis manifested by the superior vena caval syndrome early in his course. This caused confusion regarding the diagnosis, which led to bronchoscopy to look for a mass lesion. The superior vena caval syndrome has been well described in association with mediastinitis,[20(p933)] but we can find no other reports in the literature of this complication associated with sternoclavicular infection. A pleural effusion also developed in this patient that was consistent with a transudative process. This complication could be explained on the basis of associated mediastinitis causing obstruction of lymphatic and venous outflow, which has been previously reported.[21] It is surprising that these complications have not been noted in prior cases, given the anatomic proximity of the superior mediastinum and the great veins to the sternoclavicular joint.

Finally, Linscheid and co-workers reported the cases of two patients, both of whom had left upper lobe infiltrates on presentation.[5] The etiology of this is unclear, but it perhaps represents contiguous spread of infection from adjacent soft tissues resulting in a pneumonitis, as suggested by our patient, who had severe gas exchange abnormalities requiring ventilatory support.

In summary, sternoclavicular septic arthritis, albeit a rare occurrence, may present with a host of varying signs and symptoms related to the joint's anatomic proximity to the mediastinum, pleural cavity, chest wall, and great vessels. Physicians should maintain a high index of suspicion for this infection in any patient who presents with pain and swelling around the sternoclavicular joint or anterior chest wall. Supe-

Figure 2.—A computed tomographic scan at the level of the sternoclavicular joint shows a mass extending posteriorly (**arrow**), with anterior chest wall swelling and an inflammatory process of the mediastinum causing tracheal deviation.

rior vena caval obstruction may complicate the clinical picture due to mediastinitis from contiguous spread of infection. A timely diagnosis should be made with the aid of computed tomography, joint aspiration, and surgical exploration, if needed. Septic shock may develop quite rapidly, as shown by the high incidence of bacteremia associated with this syndrome.

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Alzheimer's Disease

PART OF THE REASON we do evaluations for Alzheimer's disease is because of reversible causes of dementia, and it is estimated that between 10% and 25% of those people presenting with cognitive decline *will* have a reversible component to their disease.

There is a long list of reversible causes of dementia. Drug toxicity probably leads the list, and, remember, all drugs may be psychoactive in the elderly. The big culprits are the sedative hypnotics, especially those longer-acting ones like Valium, Librium, and Dalmane. If you consider the cholinergic hypothesis of dementia, you can understand why anticholinergic medications—which are ubiquitous and found in over-the-counter cold remedies, sleeping pills like Benadryl, tricyclic antidepressants, and the antipsychotics we give demented old people—may, in fact, make them more confused.

Many medical diseases—hypo- and hyperthyroidism, for instance—are important to exclude.

Structural diseases such as subdural hematoma and meningioma: both of these usually have focal neurologic findings but may not.

Neurosyphilis has not been eradicated, and we still see patients with this disease. B12 and folate deficiency probably cause dementia.

There is also a disease known as normal pressure hydrocephalus that is considerably rarer than has been spoken of recently and is sometimes reversible.

—MARK BEERS, MD

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Clinicopathologic Conference

Rapidly Progressive Dementia Caused by Spongiform Encephalopathy

Discussants
BRUCE E. ENOS, MD, *and* HARRY V. VINTERS, MD

HARRY V. VINTERS, MD*: A 53-year-old woman, a receptionist, was in good health until six weeks before hospital admission, at which time she stopped going to work because she was "feeling bad." She had frequent episodes of dizziness and buzzing in the ears and an intermittent feeling of fullness in the ears. An otolaryngologist noted her blood pressure to be 180/96 mm of mercury. A week after her symptoms began, she was sleeping excessively during the day, irritable, extremely sensitive, unusually quiet at times, but oriented to time and person. At Christmas, about two weeks after the onset of her symptoms, she neglected to give gifts to family members, which was attributed to situational stress. A physician noted that she had an ataxic gait, slurred speech, and fell to the right when attempting a tandem gait. There was diminished ability to perform rapid alternating movements with the right hand.

At her initial hospital admission, a general physical examination showed no abnormalities. On neurologic examination she had slow speech, but she was able to follow commands and was fully oriented. Her gait was ataxic, and there was an especially pronounced difficulty in doing tandem gait, with a tendency to fall to the right. There was upward drift of the right hand on extension. The results of routine biochemical studies and a toxicology screen were normal. A lumbar puncture yielded clear colorless cerebrospinal fluid (CSF) that showed no abnormalities. An electroencephalogram (EEG) showed diffuse slowing, with some tendency for slow activity to be localized to the left cerebral hemisphere. An isotope brain scan was normal. In hospital, the patient remained independent and kept herself groomed, but she lost interest in daily activities such as reading and watching television and was indifferent to current events. She showed rapidly deteriorating memory, ambulation, and personality. Insight into her problem decreased. She had difficulty grasping objects with the right hand. She was discharged home briefly and readmitted to hospital because she had "no feeling" on the right side. She remained awake and alert but was now notably confused, with poor immediate and remote recall. Her affect was blunted, and she was unable to write or calculate but had no right/left confusion.

The patient had smoked a pack of cigarettes per day but did not abuse drugs or alcohol. She had an appendectomy in 1949 and a hysterectomy in 1968. Her family history was noncontributory. The patient's medications included conjugated estrogen (Premarin), hydrochlorothiazide, and levothyroxine sodium (Synthroid).

On physical examination 1½ months after her symptoms began, she had a blood pressure of 130/80 mm of mercury with no orthostatic change, and her pulse was 85 per minute and regular. She cooperated poorly, was agitated and hostile throughout the examination, but appeared well developed and well nourished for her stated age. She was alert but notably confused. There was poor recall for immediate, recent, or remote events. Her affect was blunted, and the patient was not hallucinating or delusional. Her speech was occasionally interrupted and nonfluent. The patient was unable to write or calculate.

Cranial nerves on examination were normal, and the fundi showed no abnormalities. A motor examination revealed that muscle tone was slightly diminished throughout. There was no focal atrophy, and no fasciculations were noted. With her upper extremities outstretched, she had pendular movements with hyperabduction of the right arm. Testing of strength was not feasible, though there was no apparent focal weakness. Deep tendon reflexes were 1 to 2+ throughout, and plantar responses were equivocal. Sensory testing was difficult apart from assessing perception of pinprick, which showed no abnormalities. She showed poor performance of finger-to-nose and heel-to-shin testing bilaterally, though this was more pronounced on the right side, and she had slight truncal ataxia. Her gait was slightly broad based, and the patient was unable to tandem walk.

Further studies in hospital included an EEG that, in addition to the diffuse slowing of the background rhythm, showed superimposed triphasic waves throughout. Assays for heavy metals (arsenic, lead, mercury) were all within normal limits. Urinary porphyrin studies showed no abnormalities. Serum electrophoresis and thyroid-stimulating hormone, tri-

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(Enos BE, Vinters HV: Rapidly progressive dementia caused by spongiform encephalopathy [Clinicopathologic Conference]. West J Med 1988 Mar; 148:313-319)

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ABBREVIATIONS USED IN TEXT

CNS = central nervous system
CSF = cerebrospinal fluid
CT = computed tomographic
EEG = electroencephalogram

iodothyronine, thyroxine, serum B_{12}, and folate levels were normal. The VDRL was nonreactive in serum and CSF, and results of serologic studies aimed at detecting an autoimmune disorder were noncontributory. Serum and CSF antibody titers to several viruses were within normal limits. The CSF myelin basic protein level was normal, and oligoclonal bands were not seen. A computed tomographic (CT) scan of the head with and without contrast was normal. Brain-stem auditory evoked potentials were unremarkable. Delayed latencies were noted on the flash visual evoked potential test. Serial EEGs showed pronounced abnormalities due to the presence of pseudoperiodic complexes in the parasagittal regions, which were at times asymmetric—that is, present in the left temporal distribution while absent on the right. This was superimposed on diffuse background slowing. Periodic and pseudoperiodic complexes with a triphasic appearance were noted, as were frequent multifocal and generalized spikes. The patient was discharged from hospital on a medication regimen that included phenytoin and multivitamins (Theragran).

Following this neurologic assessment, she survived about 22 months. During this time, myoclonic jerks were said to develop, and her dementia progressed, as did ataxia and rigidity. The circumstances of her death are unknown.

Bruce E. Enos, MD*: In summary, the case is that of a previously healthy 53-year-old woman with a subacute onset of mental deterioration and ataxia, followed by a more protracted course of progressive dementia, ataxia, rigidity, and myoclonus. The entire time span from the beginning of her neurologic deterioration to death was about two years.

Early on, prodromal symptoms began suddenly, followed by a fairly rapid change in life habits accompanied by vague symptoms of intermittent dizziness, tinnitus, and ear fullness. Over two weeks she became irritable, labile, somnolent, and forgetful. About one to two months into her course, right-sided sensory changes developed. On examination there was little in the way of objective focal findings except for some updrift of the right hand on extension, suggesting some relatively right-sided proprioceptive loss. An EEG done at that time showed asymmetric bihemispheric slowing more prominent on the left. There was a progressive dementia with changes in personality, memory, language, and cognitive function. Emotional lability, hostility, and agitation were evident. The patient subsequently had more profound dementia and ataxia, as well as superimposed rigidity and myoclonus.

Deficits noted on the neurologic examination were referable to several regions of the neuraxis. The prominent ataxia implicates involvement of the cerebellum or its connections (or both). Dementia usually reflects diffuse cortical impairment or damage to deep subcortical structures that have diffuse cortical projections. This may occur from a variety of causes to be discussed later. The myoclonus that developed later in the course may also be a reflection of cortical involvement, although disease of the brain stem or possibly spinal cord might explain this, depending on the clinical characteristics of the myoclonus.[1] Emotional lability may reflect damage to the frontal cortex or to deep limbic structures. In the absence of significant weakness, sensory abnormalities, visual field deficits, or tone or reflex changes, there was little evidence of early involvement of long tracts or fiber systems of the cerebral white matter. In summary, the clinical course and neurologic findings are most consistent with a progressive, diffuse polioencephalopathy.

The early clinical course included an abrupt or subacute onset; ataxia; focal, right-sided, subjective sensory changes; and emotional lability. Diverse causes such as acute toxic and metabolic encephalopathies, central nervous system (CNS) infection, mass lesion (including multiple metastases), and vascular insufficiency must have occurred to the physicians who first assessed this patient. Laboratory tests to confirm a metabolic derangement or heavy metal toxicity gave normal values. Lumbar punctures on at least two occasions failed to show evidence of malignant cells or inflammatory change within the CNS or subarachnoid space. A CT scan failed to show a mass lesion. Focal symptoms that began abruptly may have suggested multiple strokes, but the superimposed gradual neurologic deterioration that occurred over the next two years effectively removes this as the explanation for her decline. A vasculitis affecting small cerebral blood vessels may cause focal or diffuse neurologic signs and symptoms and may be associated with normal CSF findings.[2-4] However, there were no signs of systemic vasculitis on examination, and the protracted clinical course tends to remove an isolated CNS vasculitis from serious diagnostic consideration.

The differential diagnosis of dementia is extensive. It includes primary cerebral cortical degenerations—such as Pick's disease and Alzheimer's disease—extrapyramidal syndromes, multi-infarct dementia, viral or other infectious causes, hydrocephalus, toxic-metabolic disturbance, neoplasm (within the brain or as a remote effect of visceral malignancy), and demyelinating disease. Considering the clinical course, findings on physical examination, normal serum biochemical values, normal CSF, and the absence of a mass lesion on imaging studies, I presume that this dementia represents a noninflammatory degenerative process affecting the cerebral cortex diffusely or deep subcortical structures with diffuse cortical projections.

We are left, then, with the possibility of a storage disorder, a paraneoplastic syndrome, primary parenchymal degeneration, or CNS infection by an unconventional infectious agent as a possible cause of this patient's clinical presentation and progression. Several storage disorders such as GM_2 gangliosidosis, atypical Gaucher's disease, and ceroid lipofuscinosis may produce a late-onset polioencephalopathy with a clinical syndrome of dementia, myoclonus, ataxia, and rigidity.[5] This patient's progression and onset of symptoms at age 53 years, however, would be incompatible with these disorders. Paraneoplastic syndromes may produce heterogeneous neurologic syndromes. Various syndromes have been described affecting the cerebellum, brain stem, peripheral nerves, spinal cord and dorsal root ganglia, and the limbic system.[6,7] Pathologic changes, when present, are relatively nonspecific and include perivascular accumulation of mononuclear cells, focal necrosis of neurons, and microglial infiltrates and gliosis.[7] The inflammatory nature of this syndrome, however, is occasionally reflected in an increased number of cells or protein within the CSF, which was not seen in this patient. I am also

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unaware of reports describing patients who present with a paraneoplastic syndrome involving dementia, myoclonus, and periodic complexes on an EEG. The primary cortical degenerations causing dementia (Alzheimer's disease, Pick's disease) are unlikely considerations in this case for several reasons. Ataxia is not a feature of their presentation. Even those cases that are the most rapidly progressive are of longer duration than was the case with this patient. In addition, the syndromes usually progress with a fairly typical clinical course much different from that seen in this woman.[5]

The most likely explanation of this patient's findings would be brain infection by a "slow virus" or an unconventional infectious agent, specifically Creutzfeldt-Jakob disease. Prodromal symptoms occur in about 40% of patients with this disease and include asthenia, sleep disturbance, and depression. A gradual onset is more common than a sudden onset, but the latter may occur in about 20% of affected persons. In about 10%, the abrupt occurrence of a single symptom may even resemble a transient ischemic attack or stroke.[8,9] Focal signs and symptoms are not uncommon. The mean survival after onset is about eight months, but cases lasting two years or longer have been described.[10-12] The clinical course is marked by progressive dementia and behavioral changes. Myoclonus and rigidity typically supervene later. Serum biochemical values and results of CSF examination are normal.

The EEG findings in this case are helpful in establishing the correct diagnosis and effectively ruling out other parenchymal brain diseases that may produce dementia, such as Alzheimer's disease and Pick's disease. Pseudoperiodic triphasic waves, more prominent in the left hemisphere, appeared six weeks into the patient's clinical course. These were superimposed on a diffusely slow background rhythm. Triphasic waves are associated with relatively few clinical disorders, including metabolic encephalopathies, postictal states, and Creutzfeldt-Jakob disease.[13,14] Creutzfeldt-Jakob disease is associated with runs of pseudoperiodic triphasic waves with frequencies in the range of 1 to 2 Hz. Even considering that triphasic waves may be associated with other clinical disorders, when they occur in a patient with progressive dementia, myoclonus, and rigidity, they are virtually pathognomonic for the disease. In a vast majority of patients, they occur within 12 weeks of the start of symptoms. Triphasic waves may be more prominent contralateral to the side of major clinical involvement, as was the case in this patient.[13]

Familial or sporadic dementias with myoclonus may present in a fashion clinically indistinguishable from Creutzfeldt-Jakob disease, though they often show a more protracted clinical course extending over years. Several clinical and electrophysiologic features tend to distinguish these rare disorders from Creutzfeldt-Jakob disease.[15] Subacute sclerosing panencephalitis is a degenerative disorder characterized by a rapid onset of dementia with associated myoclonus and rigidity seen

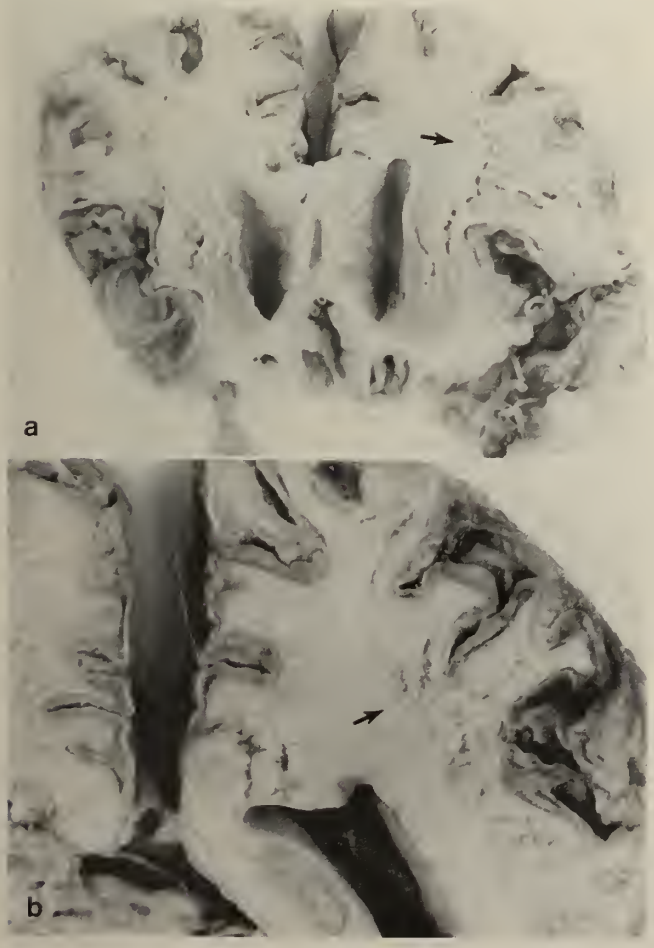

Figure 1.—Coronal sections of fixed brain from the region of the frontal lobes (a) and parietal lobes (b) show severe diffuse cortical atrophy and multifocal cystic collapse of white matter of the centrum semiovale bilaterally (arrows). Dilatation of the lateral ventricles is also seen.

Figure 2.—Midsagittal section of cerebellum shows severe atrophy throughout the vermis, most pronounced in its anterior superior portion (arrow).

late in the clinical course, but the dementia usually starts in the late first or early second decade. A CSF examination shows immunoglobulin G against the measles virus. The EEG has a pseudoperiodic pattern, but the repetitive transients are not simply triphasic and usually are complex polyspike, multiphasic discharges occurring every four to ten seconds.[14]

In summary, the clinical history and laboratory findings in this case are most consistent with Creutzfeldt-Jakob disease or spongiform encephalopathy.

Autopsy Findings

Only the brain was available for examination. The fixed brain showed diffuse atrophy of the cerebral hemispheres, most prominent in the frontal and temporal lobes with some sparing of the occipital regions. The leptomeninges were minimally opacified. The circle of Willis appeared normal. The cerebellum appeared diffusely atrophic, but the brain stem was relatively intact. Coronal sections of the cerebral hemispheres confirmed the severe, diffuse cortical atrophy throughout all lobes (Figure 1). The atrophy was focally accentuated to the point where only 0.5 to 1.0 mm of residual cortex was identified in many regions. The white matter showed multifocal encephalomalacia, with a moth-eaten appearance in a patchy distribution throughout the white matter of the centrum semiovale in both hemispheres (Figure 1). The cystic regions within the white matter were poorly demarcated, subconfluent spongy areas that varied in size from a few millimeters to several centimeters in greatest dimension. In many areas, the abnormal white matter extended to the cerebral cortex and was in continuity with areas of severe cortical atrophy. The collapse of the cortex and white matter in some regions was so pronounced as to simulate the appearance of an infarct, such as in the left insular region. Deep central grey structures including caudate and lentiform nuclei were collapsed and atrophic. Degeneration of the white matter extended symmetrically into both internal capsules and the corpus callosum. The diencephalon, however, including the mamillary bodies was relatively normal. The lateral ventricles were greatly dilated, and the third ventricle was slightly dilated. A small cavity of the septum pellucidum was identified. The hippocampi and the lateral geniculate nuclei appeared normal.

Mid- and parasagittal sections of the cerebellar hemispheres again confirmed severe, diffuse atrophy throughout the folia, most pronounced in the superior cerebellar hemispheres and especially in the anterior superior vermis (Figure 2). Horizontal sections of the brain stem showed an appearance of white matter similar to that identified above in the centrum semiovale, within the basis pontis and the cerebral peduncles, though apparently sparing the cerebellar peduncles and deep cerebellar white matter. The cerebral aqueduct and fourth ventricle were of normal size and configuration, and the pigmented nuclei (locus ceruleus and substantia nigra) were normal.

Microscopic sections of the neocortex and subcortical white matter from several regions of cerebral hemispheres showed similar features, though the severity of involvement varied from section to section. There was severe diffuse

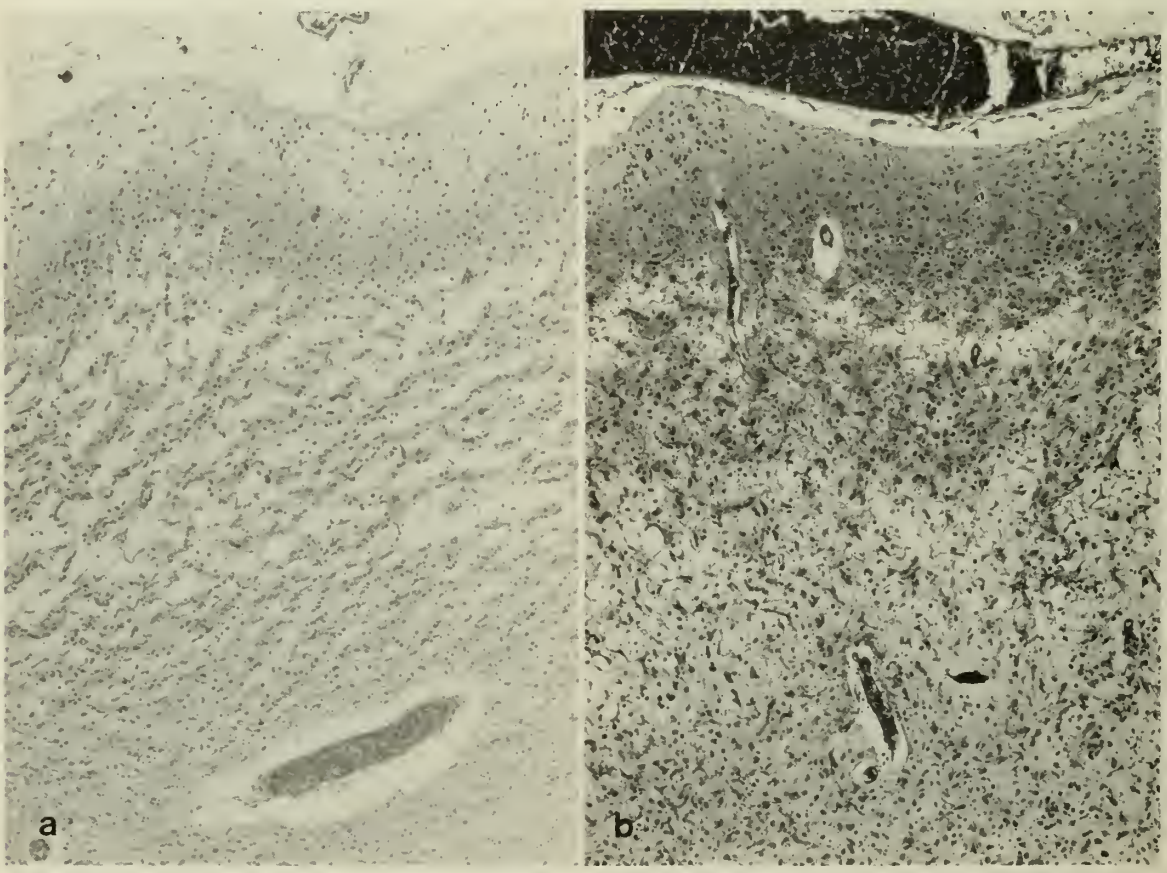

Figure 3.—Two sections of cortex from different regions, both showing virtually total loss of neurons and reactive astrocytic gliosis. In **a**, there is status spongiosus of the cortex, whereas **b** shows more characteristic vacuoles of varying sizes within the neuropil. Note the relative preservation of the molecular layer in both sections (**a**, hematoxylin and eosin, original magnification × 80; **b**, Bielschowsky's, original magnification × 80).

status spongiosus of the cortex with relative sparing of the molecular layer. The spongy change showed the appearance of either vacuoles within the neuropil or more poorly defined regions of rarefaction within the parenchyma (Figure 3). In some areas of cortex, there was essentially a total absence of neurons and, instead, the cortex had taken on a cribriform appearance (Figure 4). Substantial reactive astrocytosis was present, and the astrocytes seen were often of the gemistocytic variety.

Throughout the subcortical white matter—reflecting the changes noted at the time of brain cutting—there was severe degeneration of the white matter with apparent loss of myelin, axon cylinders, and a dense proliferation of gemistocytic astrocytes (Figure 5). All areas of the deep central white matter were affected by this process. In contradistinction to the cortex, the white matter showed numerous clusters of compound granular corpuscles (histiocytes), and an occasional macrophage contained material with the appearance of hemosiderin (Figure 6). Several thin-walled venules showed the presence of slight to moderate perivascular lymphocyte cuffing (Figure 5), and this was seen in a patchy distribution throughout the cerebral hemispheres.

The one region of cortex that was relatively spared was the hippocampus, which showed preservation of the granule cell layer and most portions of the pyramidal cell layer. The pyramidal cell layer was intact from the end-plate region distally to the level of the prosubiculum-subiculum junction, and a few intact neurons were identified in the parahippocampal gyrus. No senile plaques or neurofibrillary tangles were present in the hippocampus. The lateral geniculate nucleus was devoid of neurons and showed pronounced reactive astrocytosis. Deep central grey structures including the mamillary bodies showed severe neuron loss and spongy change with gliosis—that is, changes similar to those described above—though an occasional island of spared neurons was identified.

Sections of the midbrain showed severe degeneration that was essentially confined to the cerebral peduncles, with numerous compound granular corpuscles and reactive astrocytes identified. The colliculi showed severe neuron loss and gliosis. Oculomotor nerve nuclei were preserved, as were pigmented neurons of the substantia nigra. The pons (Figure 7) showed severe degeneration within the basis pontis, especially involving the corticospinal tracts, but severe neuron loss and astrocytic gliosis were noted within the territory of the pontine nuclei. The floor region of the fourth ventricle was relatively preserved. The medulla oblongata and pontine tegmentum showed no abnormality apart from the presence of severe secondary pyramidal tract degeneration. The inferior olivary nuclei showed slight neuron loss and astrocytic gliosis.

Sections of the cerebellar cortex showed severe atrophy, but the most severe loss was noted within the granule cell layer (Figure 8). Purkinje's cells were remarkably well preserved, but there was Bergmann's cell gliosis within the Purkinje cell layer despite the relative preservation of neurons. Severe gliosis was noted within the deep white matter of the cerebellum, which showed the loss of myelinated fibers. No area of the brain showed either parenchymal or microvascular amyloid—that is, senile plaque amyloid or amyloid-congophilic angiopathy. The only vascular abnormality noted was occasional slight to moderate fibromuscular intimal hyperplasia in a large leptomeningeal artery. The leptomeninges were otherwise normal.

Discussion

The histopathologic changes in this brain are typical of those seen in spongiform encephalopathy or Creutzfeldt-Jakob disease,[16,17] though several unusual features are present and deserve comment. The extensive parenchymal spongiform change, together with neuron loss and profound reactive

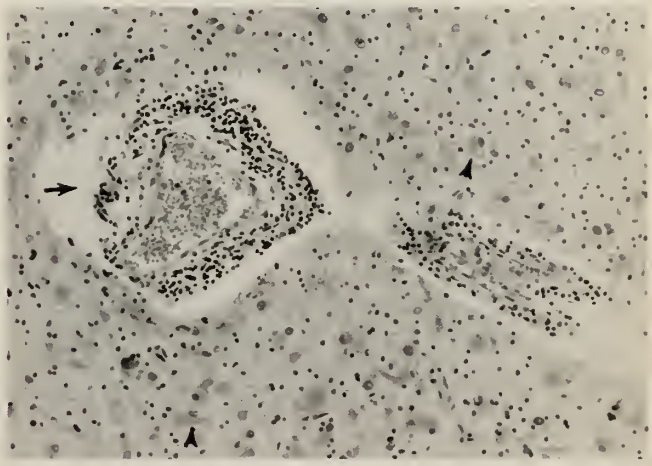

Figure 5.—The subcortical white matter shows extensive proliferation of gemistocytic astrocytes **(arrowheads)** and perivascular cuffing by mononuclear inflammatory cells **(arrow)** (hematoxylin and eosin, original magnification × 200).

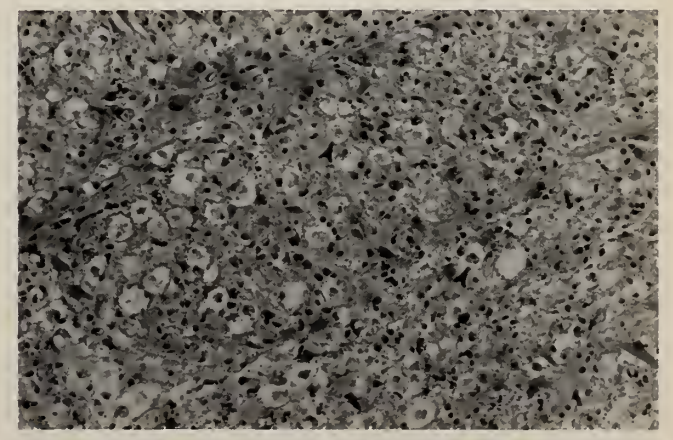

Figure 6.—A section of internal capsule shows severe degeneration of white matter, with abundant astrocytes (as in Figure 4) and many lipid-laden foamy macrophages **(arrowheads)** (hematoxylin and eosin, original magnification × 200).

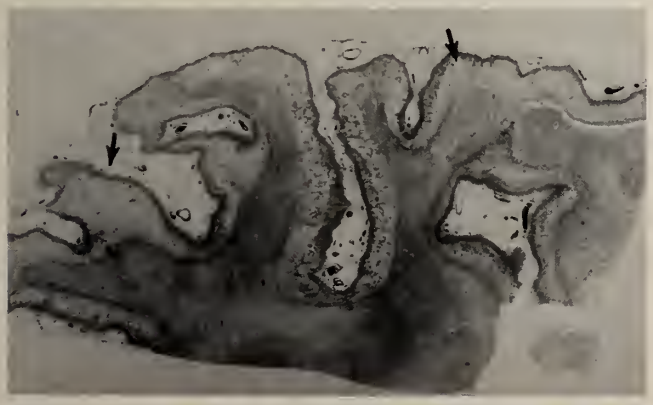

Figure 4.—A whole mount of cortex and subcortical white matter shows cribriform appearance of all areas of cortex **(arrows)** and multifocal pallor of underlying white matter (Bielschowsky's, original magnification × 5).

astrocytic gliosis, confirm the clinical diagnosis. It should be stressed that status spongiosus of the brain can be a nonspecific finding and is often associated with severe and long-standing gliosis.[18] The severe neuron loss and reactive astrocyte proliferation seen in this patient's brain are undoubtedly also partly responsible for the cribriform appearance of much of the cerebral cortex—that is, vacuoles within cell processes

Figure 7.—A section of pons is stained to show myelin. All components of the basis pontis show extreme pallor, whereas the tegmentum **(arrow)** is relatively preserved (luxol fast blue, original magnification × 5).

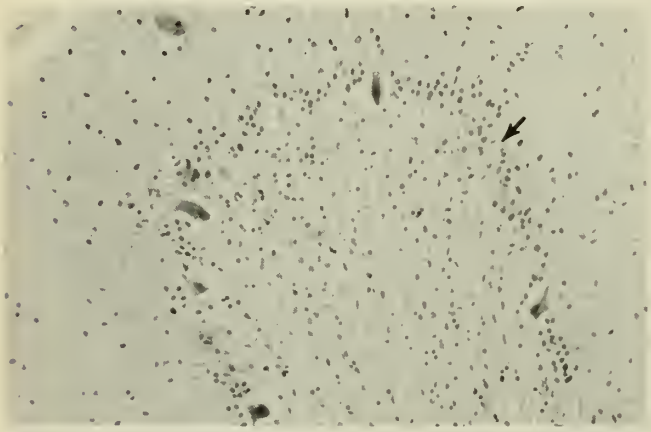

Figure 8.—The cerebellum shows severe cell loss in the granule cell layer but relatively preserved Purkinje's cells. Note the absence of spongiform change. There is proliferation of Bergmann's astrocytes **(arrow)** in the Purkinje's cell layer (hematoxylin and eosin, original magnification × 200).

(typical of this disease) were not easily identified because of the severe cortical destruction. The definitive diagnosis is made by inoculating diseased brain tissue into animals, such as primates, and effectively transmitting the neurologic disease, including inducing the appropriate histopathologic findings within the brain.[19] This procedure was not carried out in the present case. It is of further interest that this patient, with a relatively long clinical duration of disease, showed profound neocortical neuron loss—a finding that reinforces the results of a study that correlated specific histologic features within the CNS with the duration of illness in patients with this disease.[18] The relative sparing of the dentate gyrus and Ammon's horn have also been previously described.[18]

The severe degree of white matter change noted both grossly and microscopically in this patient's brain are most unusual. The gross appearances were so severe as to briefly suggest the presence of multifocal infarcts within the brain parenchyma, though histologic sections proved that the changes were not due to ischemia. Similar features of leukoencephalopathy have occasionally been noted in other patients with Creutzfeldt-Jakob disease[20,21] and were thought to represent white matter alterations that could *not* be explained purely on the basis of wallerian degeneration of axons due to neocortical neuron loss. Conversely, our case suggests that the white matter abnormality may indeed be on this basis. Several features support this contention: the profound loss of neurons from virtually all regions of the neocortex; the presence of lipid-laden histiocytes within white matter but not within the cortex, suggesting that the myelin and axon loss within the centrum semiovale postdated cell loss within the cortex; and the topography of the white matter change—that is, the corticospinal tracts were most severely involved, and other anatomic structures affected, such as pontine nuclei and pontocerebellar fibers within the basis pontis, may reflect a severe degree of transsynaptic secondary degeneration. (By contrast, ascending fiber systems, such as those in the pontine tegmentum, showed no significant abnormality.) A second unusual histologic feature was the moderately severe degree of perivascular cuffing by mononuclear inflammatory cells noted in a patchy distribution throughout the cerebral hemispheres. The essence of brain involvement by unconventional infectious agents is that inflammation does not occur.[22] Possibly this finding in the present case reflected an intercurrent brain infection by another (unidentified) conventional viral organism or simply a reaction to the severe degree of surrounding tissue breakdown.

Despite the relatively long duration of a dementing illness in this patient, she did not show the typical features of the Gerstmann-Sträussler-Scheinker syndrome.[23-25] The syndrome shares some morphologic features with the Creutzfeldt-Jakob disease but is characterized by the presence of extensive amyloid deposition within the neural parenchyma. Amyloid was not found in the brain of our patient despite a careful search for this extracellular material.

Several excellent reviews have summarized recent theories concerning the pathogenesis of the spongiform encephalopathies and the "prion" agent that is hypothesized to be important in their causation.[26-30]

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Alzheimer's Disease and Down's Syndrome

A NUMBER OF IMPORTANT POINTS have come up about Alzheimer's disease. Down's syndrome is a very significant concept—and a very important model that is giving us a lot of information about the possibilities of familial Alzheimer's.

Now, in the last five years, after 100 years of this disease being in existence, we have found out where the major lesions are in the disease—that is, the nucleus basalis, which projects to the hippocampus and to other structures—the locus ceruleus, for instance.

We have found that primarily cholinergic neurons are involved, and, therefore, all of the experimental treatments are oriented to cholinergic approaches.

There are abnormal peptides that are being discovered. The PET scan is an early diagnostic test for Alzheimer's. In addition to that, we find that there is a protein that has been isolated by Peter Davies called Alz-50, which, in preliminary studies, seems to be present in the spinal fluid of Alzheimer's patients and not in the spinal fluid of other patients.

Now, that leads us to the question of the chromosome 21. If you live to be 40 years of age and you have Down's, you will get Alzheimer's disease. Alzheimer's disease in Down's is diagnostically difficult clinically, but pathologically, it is indistinguishable.

It is amazing that you can tell if a Down's patient is demented. Even though they are initially starting at very low levels, there is clinical evidence that they have dementia.

—LESLIE P. WEINER, MD

Extracted from *Audio-Digest Family Practice,* Vol. 35, No. 40, in the Audio-Digest Foundation's series of tape-recorded programs. For subscription information: 1577 E Chevy Chase Dr, Glendale, CA 91206

Medical Staff Conference

Waldenström's Macroglobulinemia

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs Homer A. Boushey, Professor of Medicine, and David G. Warnock, Associate Professor of Medicine, under the direction of Dr Lloyd H. Smith, Jr, Professor of Medicine and Associate Dean in the School of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, School of Medicine, San Francisco, CA 94143.

RICHARD K. ROOT, MD*: *Waldenström's macroglobulinemia is a particularly interesting B-cell lymphoplasmacytic neoplasm because so many of its clinical features are due to the monoclonal IgM protein found in the serum. Curt Ries, MD, Director of Faculty Practice in Hematology and Oncology of the Cancer Research Institute, will review the current concepts of diagnosis and treatment of this disorder.*

CURT A. RIES, MD†: Waldenström's macroglobulinemia is a well-differentiated B-cell lymphoplasmacytic neoplasm characterized by the presence of a monoclonal immunoglobulin (Ig) M protein in the serum and often associated with anemia, bleeding, and hyperviscosity.

Waldenström's macroglobulinemia accounts for about 5% of all malignant B-cell disorders associated with a monoclonal protein spike in the serum or urine, and about half of patients who have a monoclonal IgM spike in the serum have this disorder. The mean age of patients presenting with Waldenström's macroglobulinemia is 65 years, and about 60% of patients are men.

Weakness and fatigue are the most common presenting symptoms, followed by bleeding, particularly mucosal bleeding such as epistaxis and gastrointestinal bleeding (Table 1). Less common are weight loss, neurologic symptoms, visual symptoms, and Raynaud's phenomenon. The most common physical findings are hepatomegaly, splenomegaly, lymphadenopathy, and ocular changes. Neurologic abnormalities, purpura, and congestive heart failure are less common.[1-6]

Anemia is the most common laboratory abnormality at the time of diagnosis. Anemia is usually mild or moderate but may be severe, requiring erythrocyte transfusions. The leukocyte and platelet counts are usually normal. Other laboratory abnormalities include an elevated serum viscosity in the majority of patients. Cryoglobulinemia occurs in about a third of patients. Bence Jones proteinuria is often found if the urine is concentrated.

There are several causes for the bleeding diathesis in Waldenström's macroglobulinemia.[7] The most important factor leading to mucocutaneous bleeding is distention of the cutaneous and mucosal capillary beds due to the increased plasma volume caused by the elevated IgM level. Platelet function is also commonly impaired because of the presence of the IgM protein on the platelet surface. The abnormal protein may also inhibit fibrin polymerization and in rare cases appears to specifically inhibit factor VIII or other clotting factors. There are also reports of clotting factors being consumed in cryoprecipitates or other precipitated protein complexes.

The anemia in Waldenström's macroglobulinemia may also have several causes. Anemia is in part due to the increased plasma volume caused by the elevated IgM level in the plasma.[8] This is a dilutional anemia and is associated with a minimal decrease in the red cell volume. Many patients with Waldenström's macroglobulinemia also have a hypoproliferative anemia due to bone marrow infiltration with abnormal lymphocytes and plasma cells.

Some patients have a hemolytic anemia due to the presence of cold agglutinins. In these patients the monoclonal IgM also has cold agglutinin activity. Finally, because of the bleeding tendency in patients with this disorder, anemia due to blood loss or iron deficiency is relatively common.

In general, there is a direct correlation between the degree of elevation of IgM in the serum, the degree of increase in serum viscosity, and the degree of plasma volume expansion and dilutional anemia.[8] Symptoms are unusual in patients with Waldenström's macroglobulinemia when the IgM level is below 3.0 grams per dl or the relative serum viscosity is less than 3.0. Increases in the IgM level above 3.0 grams per dl are usually associated with significant increases in serum viscosity and progressive symptoms. Slight increases in the relative serum viscosity, in the range of 3.0 to 5.0, are usually associated with weakness, fatigue, and exertional dyspnea, but not with severe neurologic or visual symptoms. Serum viscosity levels of greater than 5.0 usually are associated with more serious symptoms, and when the serum viscosity is greater than 10, a full-blown hyperviscosity syndrome usually occurs.

The clinical features of the hyperviscosity syndrome include bleeding, particularly epistaxis, gastrointestinal bleeding, cutaneous bleeding, and retinal hemorrhage.[9] The eye findings can include the presence of dilated or sausage-shaped veins, hemorrhage, retinal vein thrombosis, and papilledema.

Neurologic symptoms include fatigue, weakness, headache, vertigo, paresis, confusion, seizures, and coma. Finally, the hyperviscosity syndrome is associated with hypervolemia, which manifests itself clinically as congestive heart failure, although cardiac function may be completely normal.

The diagnosis of Waldenström's macroglobulinemia is usually based on the finding of a monoclonal IgM spike in the serum, which usually is greater than 1.5 grams per dl at the

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time of diagnosis. Anemia is present in most patients. Although lymphadenopathy and hepatosplenomegaly are common, these findings are variable, and their absence does not exclude the diagnosis (Table 2).

Before a diagnosis of Waldenström's macroglobulinemia can be made, other B-cell neoplasms associated with a monoclonal IgM protein must be excluded. These include chronic lymphocytic leukemia, lymphocytic lymphomas, multiple myeloma, mixed cryoglobulinemia, and cold agglutinin disease. If the IgM spike is less than 1.5 grams per dl, it may initially be difficult to differentiate Waldenström's disorder from monoclonal gammopathy of an undetermined significance.

The differential diagnosis between Waldenström's macroglobulinemia, well-differentiated lymphocytic lymphoma, and chronic lymphocytic leukemia is usually apparent; at times, however, there may be some overlap that will lead to confusion (Table 3).

In chronic lymphocytic leukemia, there must be lymphocytosis (15,000 per μl) in the peripheral blood. In Waldenström's macroglobulinemia and lymphocytic lymphomas, there may be abnormal cells present in the peripheral blood, but there is rarely lymphocytosis to this degree.

The degree of lymphadenopathy and hepatosplenomegaly is usually more subtle in patients with Waldenström's disorder than in those with chronic lymphocytic leukemia or lymphocytic lymphoma. The essential feature that usually distinguishes patients with this disorder from those with well-differentiated lymphocytic lymphoma is the degree of elevation of the IgM protein. Although a fraction of patients with lymphocytic lymphomas do have a small IgM spike in their serum, the amount of IgM is usually small compared with that in patients with Waldenström's macroglobulinemia.

The appearance of the abnormal B cells in the bone marrow or on histologic sections of bone marrow or lymph node biopsy specimens may be very similar in patients with Waldenström's disorder, those with chronic lymphocytic leukemia, and those with well-differentiated lymphocytic lymphoma. Immunologic characterization of the B cells in these three disorders may also be inconclusive. The presence of morphologically typical plasmacytoid lymphocytes, however, favors the diagnosis of Waldenström's macroglobulinemia.

Differentiating between multiple myeloma and Waldenström's macroglobulinemia is usually easy based on the type of immunoglobulin present in the monoclonal spike. The vast majority of patients with multiple myeloma have either IgG or IgA present in their serum or free light chains present in their urine. Patients with Waldenström's, on the other hand, have only IgM paraproteins. The clinical features of these two disorders are compared in Table 4. In rare cases, so-called IgM multiple myeloma has been described. These patients have IgM paraproteins, but also have lytic bone lesions and other clinical features that are usually only found in multiple myeloma.

In addition to the common presentations of Waldenström's macroglobulinemia previously noted, patients occasionally present with renal disease, pulmonary disease, or neurologic problems (Table 1). Various renal abnormalities have been described.[10] Most patients have Bence Jones proteinuria, although excretion is usually less than 1 gram per 24 hours. About a third of patients have significant nonselective proteinuria. Between 20% and 30% of patients have some degree of renal insufficiency, although, unlike the case in multiple myeloma, severe renal failure is rare. Pathologic changes in the kidney include IgM deposits in capillary loops, focal amyloidosis, interstitial infiltration with lymphocytes and plasma cells, and, rarely, immunologically mediated glomerulonephritis.[11]

TABLE 1.—*Clinical Presentations of Waldenström's Macroglobulinemia*

Common Presentations
Immunoglobulin M spike seen on protein electrophoresis
Weakness, fatigue
Anemia
Bleeding
Hepatosplenomegaly, lymphadenopathy
Uncommon Presentations
Hyperviscosity syndrome
Raynaud's phenomenon, other cryopathic symptoms
Renal disease
Pulmonary disease
Peripheral neuropathy

TABLE 2.—*Diagnostic Features of Waldenström's Macroglobulinemia*

Presence of an immunoglobulin M spike on serum protein electrophoresis and immunoelectrophoresis—usually greater than 1.5 grams per dl
Normocytic anemia usually present
Hepatosplenomegaly, lymphadenopathy (variable)
Bone marrow usually shows increased plasmacytoid lymphocytes, lymphocytes, or plasma cells
Exclude chronic lymphocytic leukemia, lymphoma, multiple myeloma, mixed cryoglobulinemia, cold agglutinin disease, monoclonal gammopathy of undetermined significance

TABLE 3.—*Differential Diagnosis of Malignant B-Cell Disorders Associated With Monoclonal Immunoglobulin M Spikes*

Diagnostic Feature	*Waldenström's Macroglobulinemia*	*Chronic Lymphocytic Leukemia*	*Lymphocytic Lymphoma*
Immunoglobulin M spike	+++	+	+
Hyperviscosity	++	−	−
Peripheral blood lymphocytosis	−	+++	+/−
Hepatosplenomegaly, lymphadenopathy	+	++	+++
Anemia	++	+/−	+/−
Bleeding	++	+/−	−
Infection	−	+	+/−
Bone marrow failure	+	++	+/−

+ = infrequent or not prominent, ++ = more prominent, +++ = very prominent, − = absent

Patients with pulmonary involvement with Waldenström's macroglobulinemia present with dyspnea, nonproductive cough, and, less commonly, chest pain.[12] Chest x-ray findings include diffuse interstitial or focal infiltrates, pulmonary nodules, hilar masses, and pleural effusions. These findings are similar to those seen in patients with advanced chronic lymphocytic leukemia and lymphocytic lymphoma.

A mixed sensorimotor neuropathy often develops in patients with Waldenström's macroglobulinemia similar to that occurring in patients with multiple myeloma.[13] The neuropathy is slowly progressive and becomes disabling in a small proportion of patients. In some of these patients, the IgM paraprotein has been shown to have antimyelin activity in vitro.

Treatment of Waldenström's macroglobulinemia depends primarily on the degree of elevation of the IgM paraprotein, which in turn determines the severity of symptoms. Patients with low levels of IgM and serum viscosity of less than 3.0 usually do not require treatment. As the IgM level increases, dilutional anemia occurs, as well as symptoms related to increased blood viscosity. Patients with serum viscosities between 3.0 and 5.0 may or may not require treatment, depending on symptoms. Patients with serum viscosities of 5.0 or greater almost always require treatment. Often patients with Waldenström's disorder attribute the most common symptoms of the disease—weakness, fatigue, and shortness of breath—to advancing age, because of the gradual onset and slow progression of these symptoms.

The therapy for Waldenström's macroglobulinemia includes erythrocyte transfusions, plasmapheresis, and chemotherapy (Table 5). Erythrocyte transfusions are most useful in patients with hypoproliferative anemias due to bone marrow infiltration. Dilutional anemia due to the increased IgM levels and corresponding increase in plasma volume is best treated by plasmapheresis. These patients have a near-normal red cell volume.

TABLE 4.—*Clinical Features of Multiple Myeloma and Waldenström's Macroglobulinemia*

	Multiple Myeloma	*Waldenström's Macroglobulinemia*
Monoclonal protein	IgG,IgA,LC	IgM
Hyperviscosity	+/−	++
Lytic bone lesions	+++	−
Anemia	+++	++
Bleeding	+	++
Infection	+++	−
Hypercalcemia	++	−
Nephropathy	++	+
Neuropathy	++	++
Bone marrow failure	++	+
Hepatosplenomegaly, lymphadenopathy	−	+

IgA=immunoglobulin A, IgG=immunoglobulin G, IgM=immunoglobulin M, LC=light chain, +=infrequent or not prominent, ++=more prominent, +++=very prominent, −=absent

TABLE 5.—*Treatment of Waldenström's Macroglobulinemia*

No treatment required—about a third of patients
Erythrocyte transfusions
Plasmapheresis
Chemotherapy
- Alkylating agents—chlorambucil, cyclophosphamide, melphalan—with or without prednisone
- Combination chemotherapy—cyclophosphamide, vincristine sulfate, prednisone (CVP); cyclophosphamide, melphalan, carmustine, vincristine, prednisone (M-2 protocol)

Plasmapheresis can be done either by the traditional bag method or by using a blood cell separator. In the bag method, a unit of blood is removed from the patient and centrifuged, the plasma is removed, and the cells are returned to the patient. This procedure can be done two to four times over a period of several hours, with removal of 600 to 1,200 ml of plasma. The main advantage of bag plasmapheresis is that it is relatively simple to do, has little risk, and does not require specialized equipment. The main limitation of bag plasmapheresis is that a relatively limited amount of plasma can be removed, so that it is not suitable for rapidly reducing the serum viscosity in patients with serious or life-threatening hyperviscosity symptoms.

Plasmapheresis using cell separators has the advantage that large amounts of plasma can be removed in relatively short periods of time. Typically, 2,000 to 4,000 ml of plasma is removed in a single pheresis session lasting two to three hours. When such large volumes of plasma are removed, volume must be replaced with plasma substitutes such as albumin or plasma protein fractions.

This type of plasmapheresis is the treatment of choice for patients with serious or life-threatening hyperviscosity. After initially controlling hyperviscosity by plasmapheresis as noted above, maintenance plasmapheresis can be done at periodic intervals using either the bag method or a cell separator to try to maintain the serum viscosity in an acceptable range.

Chemotherapy can be used to control excessive IgM production in Waldenström's macroglobulinemia and is useful in treating patients who are symptomatic and who cannot be controlled by plasmapheresis, or who require such frequent plasmapheresis that this form of therapy becomes unacceptable to them or their physicians. Chemotherapy should be initiated cautiously, as some patients with Waldenström's macroglobulinemia seem to be sensitive to chemotherapy, with granulocytopenia or thrombocytopenia readily developing. This is particularly the case for patients who have substantial bone marrow infiltration.

Various chemotherapy regimens have been used for treating patients with Waldenström's macroglobulinemia. Generally an alkylating agent, usually chlorambucil, is given initially either in a continuous low dose or in a pulsed fashion, with or without prednisone. Cyclophosphamide and melphalan have also been used. Combination chemotherapy using cyclophosphamide, vincristine sulfate, and prednisone or more intensive combinations such as the M-2 protocol (Table 5) have also been used.[14]

In general, the lower dose, less toxic chemotherapy should be tried first and the treatment escalated only if it is justified by a patient's symptoms and clinical course. High-dose intensive chemotherapy that produces severe bone marrow hypoplasia is rarely warranted in patients with Waldenström's macroglobulinemia.

The median survival is about 50 months. This survival time depends heavily on the exclusion of higher grade B-cell malignant disorders associated with IgM monoclonal proteins. Particularly, advanced chronic lymphocytic leukemia, higher grade lymphomas, and IgM myeloma must be excluded, as they have a poorer prognosis. Likewise, it is important to exclude patients with IgM monoclonal gammopathy of an undetermined significance, as these patients have a better prognosis.

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Acute Aortic Defects

MANY PATIENTS who are now being seen in the emergency room with chest pain are being considered for thrombolytic therapy. Obviously, the administration of thrombolytic therapy, whether it is streptokinase or tissue plasminogen activator in a patient with aortic dissection masquerading as a myocardial infarction, has very important implications in terms of patient welfare, as well as medicolegal implications. I suspect we may well see more and more of these reports, since the message that we are receiving from people very active in this area is that if we are going to make a significant impact and salvage myocardium during the acute phase of myocardial infarction, the thrombolytic therapy has to be given very early, and generally, it is given without catheterization and confirmation of coronary occlusion.

Now, the relationship of the site of pain to the origin of dissection is an important point. Most proximal dissections will be associated with anterior chest pain. In contrast, patients with distal dissections, type III dissections versus type I or type II, typically will present with back pain—posterior pain. Again, though, there is some variability, and the key is to ask the patient to describe the quality of pain: it is usually excruciating; it is usually tearing; it is usually maximal in intensity at outset.

Other less common presenting symptoms include syncope. In patients with dissection who present with syncope, the mechanism is almost always acute pericardial tamponade, although, rarely, significant hemorrhage into either the pleural space or the mediastinum will cause syncope. But syncope means pericardial tamponade. The presence of a pericardial effusion in a patient with a high probability of dissection is associated with an extremely high mortality. Roughly 75% of patients with pericardial effusions and dissections are dead within 24 hours if surgical therapy is not carried out.

Transient ischemic attack (TIA) and stroke, because of branch vessel occlusion; pulse loss, with or without ischemic pain; and also, congestive heart failure—these patients almost always have aortic regurgitation.

Finally, painless dissection can occur. It is very rare, and the majority of these patients at the time of presentation exhibit disturbed consciousness. If they were able to give a history, whether or not they would complain of chest pain is not clear in reviewing the history.

—ROBERT S. GIBSON, MD

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Epitomes
Important Advances in Clinical Medicine

Obstetrics and Gynecology

The Scientific Board of the California Medical Association presents the following inventory of items of progress in obstetrics and gynecology. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, research workers, or scholars to stay abreast of these items of progress in obstetrics and gynecology that have recently achieved a substantial degree of authoritative acceptance, whether in their own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Obstetrics and Gynecology of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to Division of Scientific and Educational Activities,
California Medical Association, PO Box 7690, San Francisco, CA 94120-7690

AIDS and Pregnancy

MORE THAN 50,000 clinical cases of the acquired immunodeficiency syndrome (AIDS) have been reported in the United States as of January 1988. It is now estimated that more than 2 million Americans have serologic evidence of human immunodeficiency virus (HIV) infection. The Centers for Disease Control (CDC) define the following groups of women to be at high risk for HIV infection: intravenous drug abusers, prostitutes, partners of men with HIV infection, immigrants from certain endemic areas—Haiti and Central or Eastern Africa—or partners of men from these areas, and those who received blood or certain blood products before 1985. Although women currently constitute only 10% of all AIDS cases and most of these belong to one of the defined high risk groups, the number of seropositive women may increase dramatically in the near future as heterosexual intercourse becomes a more common mode of transmission. The incidence of HIV seropositivity in pregnancy may also rise because many of these women will be in the reproductive age group.

All seropositive women should be counseled about the implications of HIV infection for themselves and their progeny. The best estimates currently suggest a 50% risk of transmitting the virus from an infected woman to her fetus. Infants with HIV infection generally become ill within the first one to two years of life and can be expected to die within two years of the onset of symptoms. Pregnant seropositive women are also at increased risk for premature labor, premature rupture of the membranes, and intrauterine growth retardation. Cesarean section does not protect a fetus from HIV infection as it does from herpesvirus infection. Breastfeeding is contraindicated because the virus has been documented in human breast milk. There are considerable risks of maternal HIV infection for the fetus. There is some disagreement as to whether pregnancy and its associated alterations in the immune system accelerate the progression of HIV disease.

Anticipating a growing number of HIV seropositive women, the CDC has recently issued recommendations for preventing HIV transmission in the course of providing health care to these women. All patients should be considered potentially infected, and appropriate precautions in handling blood, blood products, and secretions should be practiced routinely. Gloves, masks, gowns, and protective eyewear are suggested for all invasive procedures and for cesarean and vaginal deliveries. Gloves and gowns should be worn when handling the umbilical cord, placenta, or a newborn when amniotic fluid or blood is present.

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Diagnosing Breast Disease

DIAGNOSING BREAST DISEASE is based on physical examination, imaging techniques, and biopsy.

A patient, following an instruction manual, should routinely examine her breasts about one week to ten days after menses. Examination by a physician should be on at least a yearly basis with appropriate follow-up and management of suggestive lesions, especially for patients with high risk factors.

The American Cancer Society recommends a screening baseline mammogram at age 35, then a mammogram every other year from age 40 to 50, and yearly mammograms beginning at age 50. Women having screening mammograms have a reduced mortality rate from breast cancer compared with controls. Screening mammography may indicate patients requiring biopsy by revealing architectural distortion or microcalcification. This technique may also reveal a breast tissue type at a higher risk for carcinoma, indicating yearly mammographic surveillance, even if the patient is younger than 50 years.

In cases of suggestive masses, mammography may be indicated before an open biopsy is done. The presence of calcification in a mass is used to confirm removing the questionable area by a postbiopsy mammogram that reveals remaining calcification in the specimen. Also, subclinical

masses requiring biopsy may be discovered by a prebiopsy mammogram.

Ultrasound imaging of the breast is useful in differentiating solid from cystic masses, finding abscesses in patients with severe mastitis, and providing guidance for needle aspiration of deep breast cysts. Its value as a screening tool has not yet been proved.

With fine-needle aspiration, a cytologic technique is used for assessing breast lesions; its accuracy is approximately 90%. A cystic mass can be eliminated. Diagnoses are made earlier when fine-needle aspiration is used at the time a lump is first evaluated. If carcinoma is found, a patient will receive appropriate counseling and therapy earlier, and the anxiety of waiting for a surgical consultation can be substantially diminished. A negative result does not eliminate the need for a formal biopsy.

Open biopsy, using either a local or a general anesthetic, is the cornerstone to diagnosing breast disease. Needle localization and biopsy of occult lesions have greatly increased the proportion of patients with carcinomas of favorable prognosis.

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Operative Laparoscopy

OPERATIVE LAPAROSCOPY offers notable benefits compared with laparotomy: decreased patient discomfort, length of hospital stay, and cost. Laparoscopic surgical options have been enhanced by using additional puncture sites and modern instrumentation including the laparoscopic laser. Results may be comparable to those with traditional laparotomy for a wide variety of gynecologic disorders including ectopic pregnancy, hydrosalpinx, endometriosis, and tuboovarian adhesions. Specific anatomic considerations, however, such as extent of disease and adhesions, may limit the use of operative laparoscopy and necessitate a surgical approach.

Although most ectopic pregnancies are ruptured or too advanced—greater than 3 cm in diameter—at diagnosis to permit treatment to be completed solely with the laparoscope, unruptured ampullary tubal pregnancies may be treated using the laparoscope to allow tubal preservation. A linear salpingostomy is made along the antimesenteric border of the tube after its base is injected with a dilute solution of a vasopressin (Pitressin) for hemostasis. The ectopic implant can then be removed with laparoscopic forceps.

The carbon dioxide and argon lasers both have laparoscopic applications, particularly for lysing pelvic adhesions and vaporizing implants of endometriosis. The argon laser is particularly useful because its wavelength, 488 nm, is selectively absorbed by pigments (hemosiderin and hemoglobin) concentrated in endometriosis implants.

Hydrosalpinx may be treated by laparoscopic incision of the ampullary portion of the tube after its distension with saline and methylene blue. Peritubal and fimbrial adhesions are lysed by microcautery or with the carbon dioxide laser. Tubal edges can be everted with a defocused laser beam to the tubal peritoneum.

Continuing innovation, such as laparoscopic suture placement, will expand on the indications for operative laparoscopy. Large case studies in the future will establish the choice of operative laparoscopy over conventional laparotomy.

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Endometriosis—New Insights Into an Enigmatic Disorder

THE CLINICAL SYMPTOMS associated with endometriosis include pelvic pain, as well as dysmenorrhea or infertility, or both. The pathognomonic feature of this disease is the presence of hormonally responsive endometrial glands and stroma in extrauterine sites. These lesions can vary dramatically in their appearance, ranging from violaceous nodules to simple petechiae. The visible and histologic manifestations of endometriosis are remarkably prevalent and have been identified in as many as 50% of premenopausal women. Fortunately, only 10% to 15% of women seem to be symptomatically affected. Contrary to earlier reports, endometriosis has no racial or socioeconomic predilection, although a polygenic and multifactorial hereditary propensity for endometriosis has been shown.

A definitive diagnosis requires direct visualization of the endometriotic lesions. Laparoscopy is the primary diagnostic method, with confirmation by biopsy if uncertainty exists. Ancillary diagnostic modalities, such as magnetic resonance imaging of the pelvis and serum concentrations of the coelomic antigen CA-125, currently lack the sensitivity and specificity, respectively, for routine clinical application. The American Fertility Society classification system, based on the visible sites and extent of involvement, has gained widespread acceptance for staging.

Hormonal therapy for endometriosis has included high-dose synthetic estrogens, progestins, oral contraceptives, androgens and derivatives of testosterone, but many of these agents are associated with undesirable side effects. Recent clinical trials suggest that gonadotropin-releasing hormone analogues may be safe and efficacious agents to treat the disease. Continuous, nonpulsatile administration of gonadotropin-releasing hormone creates a distinct hormonal pattern, with an initial rise followed by an inhibition of gonadotropin release. The menopause-like condition brought about by long-term treatment with gonadotropin-releasing hormone analogues induces endometrial atrophy and thus provides a basis for its use in endometriosis. "Hot flashes" are a well-recognized side effect of analogue treatment, and there may be an adverse effect on estrogen-dependent bone density. Although the analogues show promise, comparative studies with other agents used to treat endometriosis-associated infertility will be necessary to determine efficacy. Only one agonist, leuprolide acetate (Lupron), is clinically available and currently approved for treating prostatic carcinoma. It is anticipated that this and additional long-acting agonists will become available in the next two to five years for the therapy of endometriosis.

Although preliminary reports are few, laparoscopic laser ablation for women with moderate to severe endometriosis

appears to be as effective as traditional surgical treatment. Advantages of laparoscopy-directed laser or electrocautery are decreased cost and morbidity for appropriate patients. For patients in whom infertility persists after ablative therapy, in vitro fertilization or gamete intrafallopian transfer may be indicated.

Areas of active investigation include assessing abnormal endocrine and immune responses in women with endometriosis, trials of combined medical and surgical therapies, and developing discriminating analyses to evaluate the efficacy of treatment.

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Mammography—The State of the Art

IN AMERICA, breast cancer will develop in one in ten women, and there will be 42,000 breast cancer deaths in 1988. Despite improvements in surgical techniques and adjunctive therapies, only screening mammography—that is, mammography done for asymptomatic women—has been able to significantly reduce breast cancer mortality thus far.

Breast cancer has been reported to be present two to seven years before detection. Because mammography has a threshold for detectability of around 2 mm, many breast cancers can be detected long before they are palpable. If the lesions are totally in situ and less than 5 mm in diameter, the 20-year survival rate is 93%. The significance to breast cancer mortality can be staggering.

The American Cancer Society's guidelines for mammographic screening are as follows:

Ages 35 to 40	Baseline examination
Ages 40 to 50	Annually or biannually, depending on risk
Over 50	Annually

Failing to diagnose cancer is a serious and frequent cause of medical liability. These guidelines have become a standard of care throughout the medical community. In certain states, for example, malpractice insurance companies levy heavy surcharges—$25,000 by one Colorado company—on physicians who do not follow these guidelines, and some attorneys are convinced they will lose any case, regardless of its merit, if the guidelines were not followed.

Despite the good news about early detection with mammography, it should be noted that approximately 10% of breast cancers are missed completely with mammography. Palpable masses, therefore, despite negative mammography results, cannot be ignored and require further workup and diagnosis. In addition, approximately 20% to 30% of questionable lesions found with mammography turn out to be cancer. This specificity may be improved with special technical advances, such as magnification, coned compression, and, perhaps, special grid techniques.

Until recently, the fear that radiation could cause malignant changes made physicians and their patients afraid of routine mammography. With modern equipment, the dose of radiation is 0.1 to 0.5 rads per breast examined. The risk of inducing cancer from this minimal dose is thought to be equivalent to smoking a quarter of a cigarette and, thus, no longer an argument against screening.

It behooves practitioners today to follow the American Cancer Society's guidelines, ascertain the quality of equipment used, and refer patients to interested, competent radiologists.

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Personal Protection Against Sexually Transmitted Diseases

THE CURRENT EPIDEMIC of human immunodeficiency virus (HIV) and other viral sexually transmitted diseases has highlighted the importance of primary prevention of these illnesses. A rapidly growing body of literature has documented several pragmatic strategies.

Behavioral messages should emphasize mutual monogamy, careful selection of sexual partners, and avoiding sexual practices, such as anal intercourse, that may carry increased risks of infection.

Clinical and laboratory studies confirm that using barrier contraceptives and spermicides confers significant protection against acquiring sexually transmitted diseases, especially when used simultaneously—such as a condom plus spermicidal foam. Latex condoms may offer greater protection than natural lamb cecum condoms. The contraceptive sponge recently has been found to protect against infection with the gonococcus and *Chlamydia trachomatis.* Sterilization of men and women provides excellent protection against upper genital tract infections.

Hepatitis B, recently recognized as an important sexually transmitted disease among heterosexuals, is the only one for which there is a safe and effective vaccine. Progress on vaccines against gonococci and HIV has been frustratingly slow.

Postcoital washing or promptly urinating after coitus has not been shown to be effective in reducing the risk of diseases transmitted sexually.

Because the hope for rapid cures of some important sexually transmitted diseases has vanished, persons at risk should modify their sexual behavior and use barrier contraceptives plus spermicides to protect themselves and their partners.

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Chorionic Villi Sampling for First Trimester Prenatal Diagnosis

OVER THE PAST FIVE YEARS, transcervical chorionic villi sampling has emerged as an alternative to amniocentesis for women who wish to have a prenatal genetic diagnosis. At present, it is done at more than 100 centers worldwide and more than 32,000 patients have had the procedure. Chorionic villi sampling is 98% successful compared with amniocentesis, which is close to 100% successful. Failures are usually due to difficult catheter placement because of cervical stenosis or uterine fibroids. Although initially popular, endoscopic sampling with forceps has been discontinued in favor of ultrasound-guided aspiration with a thin catheter. The procedure is done by passing a 1-mm flexible catheter through an undilated cervix and then, under ultrasound guidance, advancing the catheter to the implantation site where the chorionic villi are most abundant. Aspiration is done with either a handheld syringe or suction machine.

The advantage of chorionic villi sampling is that it is done between the 9th and 12th weeks of gestation compared with between the 16th and 20th weeks for conventional amniocentesis. Early amniocentesis, which is currently under investigation at several centers, is done between the 12th and 14th weeks. Furthermore, a direct chromosomal analysis of the chorionic villi will yield results in 48 to 72 hours, whereas results from amniocentesis usually require one to two weeks. Because the direct analysis is not foolproof and cannot always exclude fetal chromosomal mosaicism, some of the aspirated villi are placed in culture and analyzed in one to two weeks, similar to the analysis following amniocentesis. Results are available early enough to allow for termination of pregnancy on an outpatient basis and avoidance of midtrimester abortion with its inherent increased risk and emotional distress. A disadvantage of chorionic villi sampling is that since amniotic fluid is not obtained, the α-fetoprotein level in the fluid cannot be determined.

The major concerns of chorionic villi sampling are whether the procedure results in an increased risk of spontaneous abortion, intrauterine infection, or long-term complications such as intrauterine growth retardation. Currently the incidence of spontaneous abortion following the procedure is 3.8%. The reported incidence of pregnancy loss following conventional amniocentesis is between 0.2% and 0.5%. It is important to compare these numbers with the baseline spontaneous abortion rate in control patients who do not undergo chorionic villi sampling. Several authors have reported that this rate is between 2.7% and 6.7% in women between the ages of 35 and 40 years. More than 18,000 infants have been delivered following chorionic villi sampling, and the incidences of long-term complications such as placental disorders, premature labor, chorioamnionitis, intrauterine growth retardation, and fetal anomalies are not increased.

The risk of other complications also appears to be low. Intrauterine infection occurs in less than 1% of cases. There have been four cases of serious infections reported, however, including septic shock resulting in hysterectomy. The incidence of unintentional rupture of the gestational sac is 0.3%. An incorrect diagnosis resulting from contamination of villi with maternal decidual cells occurs in less than 1% of patients.

Chorionic villi sampling appears to be a safe procedure and one that many patients might consider preferable to amniocentesis. Ongoing studies are attempting to further delineate the efficacy and safety of the procedure. One of the avenues of investigation is to randomly assign patients for amniocentesis or chorionic villi sampling to further define the risk of pregnancy loss. Another is the introduction of ultrasound-guided transabdominal chorionic villi sampling, which has the advantage of avoiding possible infection due to vaginal and cervical bacteria. Three European centers have reported on this approach in more than 300 patients, with a pregnancy loss rate of 2.2%.

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Editorials

Is There a Lesson From History?

ELSEWHERE IN this issue is a comprehensive article by Haller describing the history of workers' compensation laws and the responses of the medical profession as these developed in America during the early decades of this century. The paper leaves it to the reader to decide how far we have come since then or to draw any parallels there might be between the profession's response to the early experiments with these laws and the reactions to some comparably fundamental experiments in health care delivery that are being tried today. When one reads this paper and thinks about what it has to say, there has to be a sense of déjà vu. Then, as now, physicians seemed to be both resisting and in the forefront of changes that were and are, in many ways, inevitable. One can only wonder if there is any lesson to be learned from the way workers' compensation developed around the turn of the century that might be useful to us today. Perhaps it is that when the medical profession clearly allies itself with the patients' best interests, it seems to be in the strongest position to be effective.

MSMW

Creutzfeldt-Jakob Disease, 1988

For 'tis the sport to have the engineer
Hoist by his own petard. . .

WILLIAM SHAKESPEARE, 1601
Hamlet

HARD WORDS FOR THE EDITORIAL SAGE!—even if he does have the good fortune to be working from the well-constructed Clinicopathologic Conference case of Creutzfeldt-Jakob disease published elsewhere in this issue. The patient, a middle-aged woman in good health and with no familial history of neurologic disease, presented with the subacute onset of dizziness, uncharacteristic behavior, with an abnormal sleeping pattern, and cerebellar signs. The illness then progressed to include a global mental deterioration, pseudoperiodic electroencephalographic (EEG) activity, and myoclonus, thus completing the characteristic triad of diagnostic elements for Creutzfeldt-Jakob disease.

Only the duration of illness was unusual, and although the diagnosis can be problematic in the 5% of cases with illnesses extending for two or more years, the early onset and relentless progression of physical neurologic signs that accompanied the dementia in this patient were a strong argument in favor of the disease. This case, then, recapitulates most of the typical features of Creutzfeldt-Jakob disease, at the same time reminding us that, atypically, its duration may overlap that of other chronic dementing processes.

To place into perspective the ease with which the diagnosis can usually now be made, it should be recalled that between 1921, when the disease was first described, and 1968, when it was discovered to be transmissible, there was an enormous conceptual confusion about it, and scores of cases were published that in retrospect comprised a heterogeneous collection of different diseases. In fact, only two of the six cases published by Creutzfeldt and Jakob themselves would today qualify for the clinical and neuropathologic criteria of Creutzfeldt-Jakob disease!

It was only by the use of primate transmission studies as the sine qua non for diagnosis that we have been able during the past 20 years to refine our diagnostic criteria to the point where today the coincidence of "typical" clinical and neuropathologic features in the great majority of cases makes the definitive verification by transmission a redundant exercise. This firmly established base has also permitted us to concentrate upon fundamental biologic questions about the nature of the agent that causes it, and since it is transmissible, how (or if) the agent can be "caught."

It has been thought for some time that the infectious particle of Creutzfeldt-Jakob disease is about the size of a small virus, and that in many respects, both in vitro and in vivo, it shows a typically viruslike behavior. However, the agent has never been visualized by electron microscopy, cannot be usefully propagated by tissue culture techniques, and exhibits an extraordinary resistance to physical and chemical inactivation. For these and other reasons, it was named an "unconventional" virus.

The viral nature of the agent has recently been called into question by the discovery of a submicroscopic fibril, at least partly composed of a β-pleated, amyloid type of plasma membrane glycoprotein that is uniquely associated with the spongiform encephalopathies, including Creutzfeldt-Jakob disease. The glycoprotein is a posttranslational modification of a normal host-precursor protein that in humans is encoded by a gene on chromosome 20. It is diffusely distributed in the brain tissue of patients with Creutzfeldt-Jakob disease and can accumulate to contribute to the amyloid plaques seen in some patients. More important, the amount of protein has been found to parallel the degree of infectivity present in purified extracts of brain.

The obvious question is whether the fibril (or its constituent protein) is itself the agent or merely a co-purifying host component of the pathologic process. An unequivocal answer will require that either a *totally* pure preparation of fibrils or protein, or synthetically prepared copies of the protein, be shown to cause disease in inoculated animals. The preparation of such material is technically difficult and is being pursued in several laboratories.

It has also been suggested that what appears to be replication may actually represent a self-cycling, autocatalytic generation of the modified protein. There are sufficient examples of this mechanism operating in normal protein biochemistry to encourage its consideration as a mechanism for the accumulation of pathologic protein in patients with Creutzfeldt-Jakob disease. In this context, some recent discoveries about the molecular biology of two other chronic dementias—Alzheimer's disease and the parkinsonian-dementia complex in Guamians—may be relevant.

The fibrils (paired helical filaments) in the amyloid plaques of Alzheimer's disease and neurofibrillary tangles of parkinsonian-dementia have been found to be composed of a single amyloid protein (distinct from the amyloid protein of Creutzfeldt-Jakob disease) that is co-localized with abnormal quantities of calcium, aluminum, and silicon. Certain aluminosilicate clays have at least a limited ability to replicate, in the sense that they can transmit information in the process of reproducing crystalline copies of themselves, and the proposal has been made that this combination of protein and "replicating clay" may be responsible for the development of

both tangles and plaques, with consequent disruption of neuronal function leading to overt disease.

It is possible that an analogous situation exists in Creutzfeldt-Jakob disease: the fibril could include, in addition to the modified glycoprotein, a mineral component similar to that of Alzheimer's disease and parkinsonian-dementia, and autocatalytic production of the protein in association with replication of a crystalline mineral component could produce an accumulation of fibrils in and around plasma membranes. These could in turn promote the observed early occurrence of abnormal lamination of membrane layers, with peeling off into the cell interior of membrane-bound vacuoles, leading to an increasing degree of spongiosus, functional impairment, and eventual cell death. This scenario is under current investigation but even if correct will not necessarily reveal the identity of the trigger to this crystalline or autocatalytic "replication," which may yet turn out to be a virus!

This brings us back to the second of the two questions mentioned earlier: how does one "catch" Creutzfeldt-Jakob disease? The surest way is to be inoculated with infected tissue—that is, iatrogenic transmission—whether in the form of inadvertently contaminated EEG or neurosurgical instruments, tissue grafts, or tissue extracts (exemplified by the current outbreak of the disease in hypopituitary patients treated with growth hormone extracted from pools of human cadaver pituitary glands). These cases represent but a small fraction of the annual mortality from Creutzfeldt-Jakob disease, however, which is about one case per million people, or some 250 cases each year in the United States alone.

After more than a decade of intensive epidemiologic research, the means by which the usual sporadically occurring disease is acquired still eludes us. On balance, the evidence does not favor the idea that Creutzfeldt-Jakob disease results from exposure to lamb or other sheep products contaminated by the closely analogous scrapie agent, and there is no evidence whatsoever to support the idea of spread from clinically affected persons to healthy contacts. Indeed, an incidence of one case of Creutzfeldt-Jakob disease per million people poses a substantial problem for almost any imaginable mechanism of human-to-human transmission. The single theoretical exception would be the silent spread of a ubiquitous infectious agent early in life, with the disease developing in "susceptible" persons only after an incubation period of several decades. In favor of this hypothesis is the fact that kuru, the other human spongiform encephalopathy, is known to have incubation periods of as long as 30 years, and there are numerous other examples of long incubation periods following infection by certain "ordinary" bacterial and viral microorganisms. There is, however, no direct evidence that this explanation applies to Creutzfeldt-Jakob disease.

An attractive alternative hypothesis would make use of observations from both the molecular biologic and epidemiologic studies of the disease. If the triggering mechanism were, instead of an infectious agent, a spontaneously occurring mutation of a regulatory gene for the host precursor protein, it might set in (slow) motion the complete train of pathogenetic events described above, eliminate the need for a contagious agent, and account for the fact that most cases occur in random fashion at about the same frequency as do spontaneous mutations. Iatrogenic and experimental transmission could simply be the result of introducing into the body an already preformed mutant "seed" molecule capable of initiating autocatalytic replication. Again, however, there is at present no evidence that such a mechanism is actually operating in this disease.

This editorial began with a quotation that referred to the irony of being blown away by one's own creation (and that may also be read as an earthy admonition against the dangers of windy speculation). It may indeed seem that the field is now heavy with hypotheses—enough to keep us busy for the next several years—but it is only fair to add that this situation exists precisely because of the accomplishments of the past 20 years. The current pace of research gives us cause to be optimistic that at least one of our own "petards" will not backfire but shoot true to the mark!

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Judging Patient Care by Outcome

THERE SEEMS TO BE a growing interest in assessing both the quality and cost of patient care by measuring outcomes of care. One would think this reasonable enough. After all, in a football game, the final outcome on the scoreboard is a clear measure of a team's success or failure. In manufacturing automobiles, both quality and cost are to a degree reflected in the outcome—that is, how well a model sells in the marketplace. A related measure of outcome is customer or consumer satisfaction with both the quality of performance and the cost of the automobile. One may then reasonably ask just how valid is this sort of conventional wisdom when it is applied to outcomes in patient care?

Those who pay most of the bills for health care, whether it is government in the public sector or business and industry in the private sector, are desperately searching for simple, objective ways to measure the quality and cost of the services or the product they are buying. Useful measures that can be computerized and subjected to statistical analysis and then used for comparisons of quality and cost would be ideal. Bureaucracies are a fact of life in both the public and private sectors of society. Actually, they are essential if things are to run smoothly, or perhaps even at all. But to function effectively, they require information or data that can be processed mechanically and by rote, according to whatever rules and regulations are prescribed. Uncertain data or too many dependent and independent variables, particularly if some of them are changing all the time, are at best poorly handled and at worst simply so confusing to the system that it cannot take all the variables into account and therefore fails to perform at all effectively. When this sort of situation prevails, it is tempting to try to find ways to fit the problem to be solved into what the more or less mechanical bureaucratic system is capable of doing, dependent as it almost has to be on statistical data, with the hope that in the process the original problem will eventually somehow be solved.

This having been said, it is evident that more attention is now being given to death rates as measures of outcomes in patient care and, by extension, to the hope that these will provide useful indices of cost effectiveness in patient care, by which is meant the relationship of quality and cost to outcome. In other words, could death rates somehow be an answer to the question, what are the payors getting for their money?

The federal Health Care Financing Administration (HCFA) has recently released a list of death rates at each of the 6,000 hospitals that care for Medicare patients and has compared each hospital's mortality rate with the HCFA's calculation of what could have been expected for that hospital, given the mix of patients it is known to have treated. This was done with an apparent sense of real accomplishment, by the way, in spite of strong statements from the American Medical Association, the American Hospital Association and the Joint Commission on Accreditation of Healthcare Organizations, and others in positions of knowledgeable responsibility, to the effect that these data had no established relationship to the quality of care, and that the data as released were therefore misleading. It remains to be seen what effect this unprecedented action by a hard-pressed federal bureaucracy will have on the public or the profession or whether death rates will be equally simplistically applied to patient care outcomes in other settings. But, admittedly, death rates are readily available, can be easily computerized, analyzed statistically, and used to make comparisons.

Perhaps more to the point, measuring death rates as outcomes in patient care misses the mark. It is sort of like comparing apples and oranges. Data, statistics, or comparisons about death rates are not the same thing as how well individual patients are served under the given circumstances, or how well the patient or consumer is satisfied with the care received and its outcome. Death is inevitable for everyone and will occur sooner or later in spite of everything that is done. Medical care can never change this. Where a death occurs—in a hospital or not—can at the very best be only a poor measure of the quality or cost or even the outcome of the care rendered.

There is already a long list of simplistic approaches that have been tried to solve problems of assuring quality and containing cost in patient care. None have worked. Counting death rates and publicizing them may appear to be an imaginative answer to a bureaucratic challenge, but it can only turn out to be yet another unduly simplistic approach to a very complex problem. Predictably, it too will not work, but it will surely add something, perhaps a little or perhaps a lot, to the cost of medical care and to a further misunderstanding of what medical care really seeks to achieve for a patient. The medical profession, both individually and collectively, has a lot of educating to do.

MSMW

Palinopsia Due to Nonketotic Hyperglycemia

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PALINOPSIA is a distortion of processing in the visual system in which images persist or recur after the visual stimulus has been removed.[1,2] In a related condition, allesthesia, visual images are transposed from one half-field of vision to the other.[3] Both conditions are well described but rare.[1-13] Controversy has arisen about whether the pathophysiologic mechanism of palinopsia is a partial seizure[3,4] or due to a "release phenomenon."[5,6] The transitory nature of palinopsia associated with persistent neurologic lesions is also remarkable, suggesting the interaction of more than one causative factor. We report here the case of a patient with visual hallucinations, palinopsia, allesthesia, and loss of spatial orientation. These symptoms were caused by focal seizures due to nonketotic hyperglycemia. Hyperglycemia may be a frequent causative factor in palinopsia. This has important practical and theoretic consequences.

Report of a Case

The patient, a 57-year-old right-handed rancher, had the sudden development of a right homonymous hemianopia. During the subsequent three days, he had peculiar spells from one to three times per hour and persistence of the field cut. The spells lasted three to six minutes each and usually consisted of visual hallucinations followed by a left parietal headache that was intensified by coughing. On several occasions, including one witnessed in the emergency ward, the spells culminated in a motor seizure, manifested by jerking, eye deviation leftward, interruption of consciousness, and postictal confusion. A partial seizure arising from the left occipital lobe was confirmed by an electroencephalographic (EEG) recording during one of the patient's typical visual hallucinations. He described a feeling of spatial disorientation and poor memory, particularly severe while the episodes were in progress. He could not give simple directions to his home nor find his way out of the physician's office. Because he could give an accurate medical history and carry on a normal conversation between seizures and because he could clearly describe the visual phenomena while they were occurring, he seemed to have focal brain dysfunction rather than a more generalized impairment or an acute confusional state.

The visual phenomena were complex and occurred together. All of the spells included flickering spots resembling a 4th of July fireworks display of "beautiful red, gold, and black sparkling lights" that would increase in size and number in the right visual field. Frequently during the time the "fireworks" were present, he had hallucinations of objects that had actually been present in his left visual field also appearing and persisting in the blind right visual field. For example, on one occasion while his physician was standing quietly on the left side of his bed during a spell, the physician's image suddenly appeared on the right side of the bed as well, in the patient's sightless hemifield. The image persisted on the blind side even when the physician moved behind the patient. Other objects the patient could see on his left shifted to the blind right side and persisted in a similar fashion during other attacks. The palinopsia (persistence) and allesthesia (transposition) always occurred together, and they did not occur in the absence of flickering lights, although the flickering lights did at times occur without the other phenomena.

Overshadowed by his dramatic visual symptoms was a history of a 10-kg (22-lb) weight loss and excessive thirst in the preceding month. He had a past history of hypertension. By examination, his neurologic abnormalities were limited to the perceptual phenomena and dense right homonymous hemianopia to confrontation testing already described. Visual acuity, extraocular movements, pupillary reactions, and other cranial nerve, motor, reflex, and sensory testing were normal.

A computed tomographic head scan was normal. His blood glucose level was 609 mg per dl (33.8 mmol per liter), serum sodium was 130 mEq per liter (130 mmol per liter), and serum potassium was 4.7 mEq per liter (4.7 mmol per liter). A glycosylated hemoglobin was 15.3% (0.153) (normal range, 5% to 9% [0.05 to 0.09]). Other biochemical testing was unremarkable. His visual symptoms and seizures ceased with control of the blood glucose level, first with insulin, then with oral hypoglycemic agents, and finally with diet alone. No anticonvulsant drugs were required. His visual field returned to normal in two days after control of the blood glucose. In four years of follow-up, he has had no recurrence of seizures or palinopsia. His diabetes remains controlled. On neurologic examination there are no abnormalities and formal visual field testing is normal.

Comment

Palinopsia is a rare phenomenon, and its mechanism is disputed. There may be a number of mechanisms for palinopsia in general, and more than one factor may be involved in any single patient. Much of the trouble in unraveling the causes of palinopsia lies in its rare and transient occurrence. Discussions in the literature are based on incomplete investigation, which is unavoidable in most instances.

Bender and colleagues[2] suggested four possible mechanisms for palinopsia: visual aftersensations, sensory seizures, hallucinations, and psychogenic elaborations or fantasies. Subsequent observers have raised other possible mechanisms, including "release hallucinations"[5,6] and migraine.[11]

We think that our patient's hallucinations, palinopsia, allesthesia, visual field defect, and spatial disorientation were caused by seizures triggered by nonketotic hyperglycemia. A number of reversible neurologic disorders are associated with nonketotic hyperglycemia, including confusion, hallucinations, hemianopia, sensory deficits, hemiparesis, aphasia, and

(Johnson SF, Loge RV: Palinopsia due to nonketotic hyperglycemia. West J Med 1988 Mar; 148:331-332)

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No reprints are available.

focal motor seizures (epilepsia partialis continua).[14-16] Our patient's neurologic abnormalities seem to be part of that array. Most of the neurologic abnormalities associated with nonketotic hyperglycemia revert to normal with correction of the hyperosmolar state, as in our patient.

Although hyperglycemia has been observed with palinopsia before,[5,7] its actual significance seems to have been little appreciated. In the 39 cases of palinopsia reviewed in this discussion,[1-13] the reports specifically mentioned the presence or absence of diabetes mellitus or hyperglycemia in only five instances.[5-7] Of those, two of the patients had normal glucose levels, one had diabetes mellitus but normoglycemia during palinopsia, and two had pronounced elevations of blood glucose levels. These latter hyperglycemic patients had reported blood glucose values as high as 699 mg per dl (38.8 mmol per liter) and 534 mg per dl (29.6 mmol per liter), respectively.[5,7] These elevated glucose levels are within the range known to cause epilepsia partialis continua.[14] Adding our case, 50% of patients with palinopsia in whom the glucose level was reported had substantial elevations. This suggests that palinopsia not uncommonly may be triggered by hyperglycemia.

In our patient, the mechanism of palinopsia appeared to be ictal. Palinopsia associated with seizures has frequently been noted in the articles reviewed here. Of 39 patients reported with palinopsia, 25 either had EEG evidence of or were observed to have seizures associated with palinopsia or responded to anticonvulsant therapy. Of these 25, 13 certainly had ictal palinopsia and another 7 had abnormal but nonparoxysmal EEGs. Considering that a surface EEG may be false-negative even during an ictus, an epileptic mechanism appears to be operative in most patients with palinopsia.

In addition to clinical observations, experiments indicate that serum hyperosmolarity and brain dehydration can induce seizures, given a potentially epileptogenic focus.[17] Our patient had no identifiable structural abnormality of his brain, in contrast to the experimental situation and most patients with epilepsia partialis continua due to nonketotic hyperglycemia.[14-17] The two previously reported cases of hyperglycemia with palinopsia did show structural pathology.[5,7] In our patient, the hemianopia and spatial disorientation persisted longer than the "fireworks," palinopsia, and allesthesia. We assume the more persistent manifestations represented a "Todd's paralysis." All of the visual phenomena cleared within two days after treatment of hyperglycemia, supporting this explanation.

Nearly all reported cases of palinopsia (34/39 or 87%) are associated with a homonymous field defect. The defect is often caused by tumor, arteriovenous malformation, hemorrhage, stroke, or trauma. When an anatomic lesion is found by computed tomography or a pathologic examination, it is usually situated at the junction of the occipital, parietal, and temporal lobes, more often in the right hemisphere than the left. When palinopsia is associated with migraine[11] or hyperglycemia (this report), however, no identifiable anatomic lesion need be present.

As for other pathophysiologic mechanisms, there are similarities between palinopic images and normal visual afterimages in some instances, but there are also differences.[2,8,12] Even if palinopsia is due to "exaggeration" of the normal afterimage process, that implies some abnormal mechanism—but what is it? The analogy does not really broaden our understanding of palinopsia or its management. Likewise, the idea of "release hallucinations," similar to the hallucinations of sensory deprivation,[5,6,8,12,18,19] serves mostly to help define a nonictal category of palinopsia but does not give a clue about the neurophysiology involved. No cases of palinopsia have been reported in psychosis, so delusions or psychiatric fantasies are unlikely explanations. As the neurophysiologic basis of migraine is better defined, the results will undoubtedly be relevant to some cases of palinopsia. It is clear at the present level of our knowledge, however, that palinopsia is a dysfunction of the association areas at the junction of temporal, occipital, and parietal lobes, is frequently an ictal phenomenon, and can be triggered by nonketotic hyperglycemia.

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An Unusual Cause of D-Lactic Acidosis

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D-LACTIC ACIDOSIS has been well documented in patients with the short-bowel syndrome.[1-4] Abnormal colonic bacterial flora have been found to be responsible for the D-lactic acid production, and symptoms can be treated with enteric antibiotics. We report an unusual case of D-lactic acidosis caused by a mechanism not previously described.

(Nghiem CH, Bui HD, Chaney RH: An unusual cause of D-lactic acidosis. West J Med 1988 Mar; 148:332-334)

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Report of a Case

The patient, a 29-year-old man with mental retardation associated with hydrocephalus, severe kyphoscoliosis, and quadriplegia, had had dysphagia with malnutrition for one year. He had been fed through a nasogastric tube an elemental diet that included in 237 ml (8 oz) 250 calories, 33.1 grams carbohydrate, 14.5 grams protein, 5.5 grams fat, 220 mg sodium, 490 mg potassium, and 625 mosm. This was a temporary measure while awaiting a percutaneous endoscopic gastrostomy for feeding purposes. When the gastrostomy was accomplished, feeding was started on the tenth postoperative day with a similar formula but administered at 50% strength at 25 ml per hour. The feeding was increased progressively in strength and amount and was well tolerated at the rate of 100 ml per hour. On day 54 after the gastrostomy placement, the original mushroom-type gastrostomy tube was replaced with a number 16 French Foley catheter. The feeding was again given continuously at the same rate.

Six hours after feeding was recommenced, the patient started having one to two episodes of loose stools per day. The loose bowel movements became profuse two days later and consisted of five to eight yellow, watery stools per day. His vital signs remained normal, with temperature 37.4°C, blood pressure 100/80 mm of mercury, heart rate 80 per minute, and respirations 20 per minute. Serum electrolytes and arterial blood gas determinations showed an acidosis with an anion gap of 27 mEq per liter (Table 1). Renal and liver function tests were within normal limits. Stool culture and stool swab were negative for pathogens, and examination for ova and parasites was negative, although a special culture for atypical bacteria was not done. There was no evidence of primary cardiovascular, renal, or hepatic abnormality; ischemia; neoplasm; or diabetes mellitus. Because of persisting diarrhea, the tube feeding was discontinued and the patient was maintained on fluids given intravenously. Within six to eight hours, the diarrhea subsided. The metabolic acidosis was corrected with an intravenous infusion of bicarbonate.

After the patient stabilized, and with the tube left unadjusted in place, the formula feeding was restarted at 25 to 50 ml per hour. In six to eight hours, severe diarrhea again developed, followed by metabolic acidosis with lethargy, flaccidity of the extremities, hypothermia, bradycardia, and hypotension. His temperature was 35°C, blood pressure 90/60 mm of mercury, the heart rate between 46 and 50 beats per minute, and rhythm was sinus. There were no localizing neurologic signs. Serum electrolytes and arterial blood gas measurements again showed a severe metabolic acidosis with an anion gap of 30 mEq per liter (Table 1). There was no evidence of ketones in the blood or urine. The serum D-lactic acid level was 5.7 mEq per liter (normal = 0), and the urine D-lactic acid value was 200 mEq per liter (normal = 0). An electroencephalogram was moderately abnormal, with mixed slow and fast rhythms and a suggestion of a right central irritative process.

A barium study of the gastrostomy tube showed kyphoscoliosis, a hiatal hernia with an intrathoracic stomach, and the catheter tip in the transverse colon (Figure 1).

The feeding tube was then removed. The patient was treated with an intravenous infusion of bicarbonate. No antibiotics or *Lactobacillus acidophilus* were given. The diarrhea stopped within six hours and did not recur. The patient recovered and tolerated well the formula feeding at 100 ml per hour via a nasogastric tube. He underwent a laparotomy for a feeding gastrostomy two months later. Since then, he has continued to do well and has gained weight satisfactorily.

Comments

This patient's clinical findings resemble those of patients with D-lactic acidosis resulting from the short-bowel syndrome, either after extensive small bowel resection[1,2] or after a jejunoileal bypass operation for obesity.[3,4] The findings have included metabolic acidosis with lethargy, weakness, dehydration, and occasional hypotension. The syndrome may be suspected when there is an increased anion gap that cannot be explained by uremia or ketonemia. It is confirmed by elevated levels of D-lactic acid in serum and urine. Stool cultures have had high counts of non-spore-forming anaerobic bacteria including *Bifidobacterium, Lactobacillus,* and *Eubacterium.*[3] Fermentation by these colonic organisms produces D-lactic

TABLE 1.—*Laboratory Findings During 2 Episodes of Diarrhea*

Laboratory Values	*Episode 1*	*Episode 2*	*Normal*
Bicarbonate, mEq/liter	7.00	12.00	25±4
Anion gap, mEq/liter	27.00	30.00	8-14
pH	7.27	7.21	7.40
Lactic dehydrogenase, units/liters	..	61.00	47-140
D-Lactate			
Blood, mEq/liter	..	5.70	0
Urine (spot), mEq/liter	..	200.00	0

Figure 1.—A supine film was taken with the patient held in a position to minimize his usual fetal position and pronounced scoliosis. The stomach, with nasogastric tube still in place, is largely intrathoracic. The tip of the Foley catheter is located in the transverse colon **(arrowhead).**

acid,[1-3] and absorption of fermentation products into the blood causes the acidosis.[5] Administering vancomycin hydrochloride or neomycin can normalize the colonic flora, with resolution of the D-lactic acidosis.[1,3,4] Schoorel and coworkers in 1980, instead of using antibiotics, recolonized the fecal flora with gram-negative bacteria with satisfactory results.[2]

Duran and associates in 1979 described a case of D-lactic aciduria in a mentally retarded child who had neither intestinal disease nor had had a bowel operation.[6] A similar case of D-lactic acidosis was recently reported in a 60-year-old man who had not undergone a surgical procedure of the bowel and did not have a history of diarrhea.[7] The source of D-lactic acid in those two cases is speculative.

In the case reported here, there was no evidence of abnormal colonic flora. The treatment consisted of neither dietary change, administration of antibiotics, nor recolonization of the fecal flora. Removing the gastrostomy tube, which had been misplaced in the transverse colon, resolved the D-lactic acidosis and the diarrhea.

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Repeated Pentostatin (2′Deoxycoformycin)-Induced Remissions in a Patient With Advanced Chronic Lymphocytic Leukemia

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Because of its prevalence and relatively favorable prognosis (median survival of more than five years), chronic lymphocytic leukemia (CLL) is the most common type of leukemia in the western world.[1] In advanced disease, combination chemotherapies including alkylating agents and steroids produce responses in more than 60% of patients.[2-8] More aggressive regimens have not produced superior results and have been associated with increased morbidity.[9,10] Most patients eventually become refractory to standard agents and die of complications related to overwhelming systemic disease. Treating advanced disease is very difficult because of severe anemia, thrombocytopenia, and neutropenia that are often made worse with cytotoxic therapy. There is a need to identify new effective agents for treating this disease. We describe the case of a patient who, despite previous treatments with multiple regimens, had repeated near-complete remissions following brief courses of the intravenous (IV) administration of pentostatin (2′deoxycoformycin).

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ABBREVIATIONS USED IN TEXT

ADA = adenosine deaminase
CLL = chronic lymphocytic leukemia
Ig = immunoglobulin
IV = intravenous

Report of a Case

In 1973 at age 59, chronic lymphocytic leukemia was diagnosed in this man. The diagnosis was later confirmed by the typical clinical syndrome and the classic immunologic phenotype with CLL cells expressing immunoglobulin (Ig) M and IgD with only λ light chains and the T65 antigen.[11,12] Between 1973 and 1977 he received an undefined amount of chlorambucil. From 1977 to 1985 he was followed at the San Diego Veterans Administration Medical Center. His disease indices and therapies during that period are shown in Figure 1. In 1979 he had progressive anemia with an increasing lymphocyte count. The monthly administration of chlorambucil was started at single doses of 30 to 40 mg per m^2 and prednisone at 20 mg per day for five days each month. He had a good response but in June 1979 was admitted with respiratory failure and hilar adenopathy. Transbronchial biopsy tissue was histologically consistent with a drug-induced hypersensitivity reaction. A regimen of daily prednisone was started, and his respiratory condition returned to normal. When his disease began to progress, the prednisone therapy was discontinued.

Therapy was restarted with cyclophosphamide, 750 mg per m^2 given IV on day 1; vincristine sulfate, 2 mg given IV on day 1; and prednisone, 80 mg a day by mouth for seven days in three-week cycles. He had a good response, but after six cycles respiratory failure and hilar adenopathy again developed, attributed to a recurrent lung hypersensitivity reaction due to alkylating agents. With the discontinuation of therapy, all symptoms disappeared; the vincristine and prednisone regimen was later discontinued because of disease progression.

By late 1981, he had accumulated a substantial tumor burden. Experimental therapy with a murine monoclonal antibody, T101, was given without a sustained response.[13] He was then given a single agent, bleomycin sulfate, 15 units IV weekly, again with a good response. This, too, had to be discontinued, however, because of respiratory difficulty. After his disease progressed, he had additional trials of T101 monoclonal antibody therapy followed by a regimen of fluorouracil, without response. Splenic irradiation, bleomycin-vincristine, prednisone, and cyclophosphamide were given serially with some decrease in tumor burden, but they also produced severe thrombocytopenia and transfusion-dependent hypoplastic anemia.

In November 1983 he received the investigational agent, pentostatin (2′deoxycoformycin; Parke-Davis, Division of Warner-Lambert Company, Ann Arbor, Michigan), at a dose of 4 mg per m^2 IV. He received two weekly doses accompanied by an immediate decrease in the lymphocyte count and resolution of his lymphadenopathy. He continued to have anemia with severe neutropenia and thrombocytopenia; a bone marrow examination revealed a severely hypoplastic marrow with a few residual lymphocytes. Two months later, following a pronounced reticulocytosis, his hematocrit and platelet count returned to normal. Despite normal leukocyte and differential cell counts and resolution of all measurable disease, a true complete remission was not obtained based on lymphocyte immunologic phenotyping that showed persistence of the malignant clone.[14] His leukocyte count remained in the normal range for six months. When his tumor burden began to increase, a single 4-mg-per-m^2 dose of pentostatin was given in October 1984. There was an immediate decrease in all measurable tumor, and the leukocyte count remained in the normal range for five months.

No further treatment was given until August 1985. At that time a single infusion of pentostatin decreased the leukocytes from 113,000 per μl to 3,800 per μl in less than a week. As with previous treatments, there was no toxic reaction except for mild nausea and vomiting and some malaise. This time his leukocyte count remained in the normal range for two months. He was retreated in October 1985 with a single injection while his leukocyte count was still in the normal range, but the differential count showed persistent lymphocytosis.

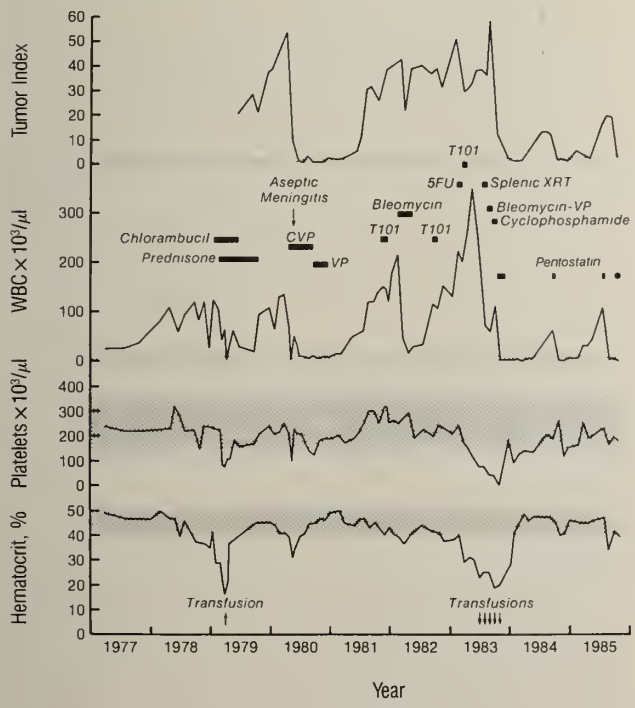

Figure 1.—The graphs depict the clinical course of this patient with chronic lymphocytic leukemia. The tumor index was calculated by adding the sum of the products of cross-sectional diameters of the largest lymph nodes in bilateral cervical, axillary, and inguinal regions, plus the number of centimeters below the left costal margin of the spleen. The shaded areas represent the normal range for each measurement. CVP = cyclophosphamide, vincristine sulfate, and prednisone, 5FU = fluorouracil, T101 = T101 murine monoclonal antibody, VP = vincristine sulfate and prednisone, WBC = leukocyte count, XRT = radiation therapy

Shortly thereafter, while in clinical remission, the patient was admitted to hospital for a severe autoimmune hemolytic anemia that required intensive care. Corticosteroid therapy was started. *Staphylococcus aureus* bacteremia developed, and the patient responded with a granulocyte count of more than 20,000 per μl. Subsequently he had an apparent drug-induced agranulocytosis that resolved within four days of discontinuing cefazolin therapy. By then, however, he had gram-negative sepsis and respiratory failure and died after six weeks in hospital. A bone marrow study done during his neutropenia showed erythroid hyperplasia but no evidence of chronic lymphocytic leukemia other than one lymphoid aggregate. There was no recurrence of lymphocytosis or lymphadenopathy during the hospital stay. Thus, he died while in a clinical remission of his leukemia, although the immune hemolytic anemia, which precipitated a series of complications leading to his demise, was probably due to the persistent underlying immunologic defects associated with CLL.

Discussion

Many studies have verified the correlation between clinical stage in CLL and survival,[15-17] although some authors have suggested that patients who respond to chemotherapy do live longer.[18] This case is noteworthy because of the dramatic remissions that were obtained with the use of pentostatin despite previous chemotherapy with six different agents, splenic irradiation, and experimental immunotherapy. With only sporadic retreatment, this patient maintained an excellent performance status for two years after being treated at a far advanced stage of disease. The quality of this remission and the limited therapy required to achieve it deserve special emphasis. This patient, who was transfusion-dependent and had severe thrombocytopenia, apparently on the basis of marrow replacement rather than an immune basis, regained completely normal blood values after receiving pentostatin. Whereas previous therapies had resulted in several admissions for marrow suppression and infections, once this man had achieved his initial remission, repeated therapy was not required and he had no secondary complications from the chemotherapy.

Pentostatin is a nucleoside analogue produced by *Streptomyces antibioticus.*[19] It is a potent inhibitor of adenosine deaminase (ADA), an enzyme in the purine salvage pathway responsible for deamination of adenosine to inosine and deoxyadenosine to deoxyinosine. The observation that children with congenital ADA deficiency had lymphopenia and immunodeficiency led to the suggestion that ADA might be required for lymphocyte proliferation. Thus, it was postulated that an inhibitor of ADA such as pentostatin might be useful in the treatment of lymphoproliferative disorders. In vitro, in the presence of deoxyadenosine, pentostatin induces cytotoxicity associated with increased cellular levels of deoxyadenosine triphosphate[20,21] that leads to decreased DNA synthesis by feedback inhibition of ribonucleotide reductase.[22,23] Pentostatin, however, is also toxic to nonreplicating cells[24,25]; thus, the mechanism of toxicity is not entirely due to deoxyadenosine triphosphate effects on DNA synthesis.[23] Pentostatin plus deoxyadenosine induces DNA strand breaks in nondividing lymphocytes,[26] but the mechanism of DNA break is unknown. Although pentostatin is generally more toxic to T lymphocytes, which have higher levels of ADA than B lymphocytes, it is toxic to CLL cells as well.[27,28] Other mechanisms of cytotoxicity are probably in-

volved, in that CLL cells have lower ADA activity than normal lymphocytes,[29] but adenosine and its analogues are more toxic to those cells than to normal lymphocytes.[30]

Although initial pentostatin trials from England were unassociated with toxicity, further studies have shown substantial side effects.[31-38] Phase I studies in the United States in children with leukemia and adults with lymphoproliferative disorders and other malignant diseases at doses of 0.25 to 1.0 mg per kg per day for three to five days were associated with nephrotoxicity; pulmonary edema; hepatic toxicity; and severe central nervous system toxicity, including lethargy, confusion, seizures, and coma.[31-34] These reactions were generally reversible when the drug therapy was discontinued. Lower doses, such as 4 mg per m^2 given IV for three days in cases of cutaneous T-cell lymphoma and 4 mg per m^2 given IV weekly in patients with CLL have been much better tolerated.[33,35,38] CLL cells have much lower levels of ADA; thus, smaller doses of pentostatin can produce a clinical effect. Grever and co-workers reported one complete response in seven previously treated patients and no significant toxicity.[37] They recently reported on treatment of 28 patients with CLL, with five objective responses and no significant toxicity.[39]

As shown by these other studies, not all patients with chronic lymphocytic leukemia can be expected to have a dramatic response to the administration of pentostatin. Phenotypically, this patient had the classic form of the leukemia, with cells that expressed IgM and IgD λ immunoglobulin on their surfaces as well as the T65 antigen.[11,12] This phenotype was unchanged throughout his treatment course, and, even at times of clinical complete remission, circulating surface immunoglobulin-positive/T65-antigen-positive cells could be detected in the circulation.

Another interesting historical feature of this patient is that he had responded to various approaches with chemotherapy and had not clearly become resistant to these agents. Rather, their use had to be discontinued because of severe pulmonary hypersensitivity reactions. Thus, he may have been potentially more responsive to pentostatin than a patient who had become refractory to standard chemotherapy agents. In the other single-institution trials of the use of pentostatin in CLL, most patients have been heavily pretreated or refractory to prior chemotherapy.[33] In view of the response of this patient, the issue of enhanced responsiveness in previously untreated patients might be raised.

Another unique feature of this patient was that he had received several treatments with the murine monoclonal antibody T101. While this antibody has not produced significant clinical remissions in patients with CLL,[13,40] it is conceivable that treatment with this agent sensitized cells in some manner so that they were more susceptible to pentostatin. This is particularly intriguing in view of the activity of pentostatin and CLL in T-cell diseases, and the fact that the T65 antigen is specific for T cells but it also reacts with B-cell CLL.[11]

Finally, in vitro this patient's cells were exquisitely sensitive to pentostatin, with a 50% lytic concentration of 0.27 μmol per liter on day 4. His cells had relatively high levels of adenosine deaminase activity at around 6 μmol per liter per minute per 10^{10} cells.[20] It may be that CLL cells from different persons are heterogeneous for susceptibility to ADA inhibition by pentostatin. If additional investigation supports this association, there may be an in vitro assay predictive of a chemotherapy response that would be more easily reproduced and more reliable than the disappointing clonogenic assay.[41] In fact, a regimen of fluorouracil was tried in this patient because of promising results in a CLL clonogenic assay (courtesy of Raymond Taetle, MD), but there was no response clinically.

The dramatic responses achieved in this patient with minimal treatment were particularly gratifying in contrast to the usual experience in such patients who have been heavily pretreated and who have anemia and thrombocytopenia. Additional studies in untreated and minimally treated patients with CLL seem appropriate on the basis of this experience and that in chronic lymphocytic leukemia, hairy cell leukemia, and other B-cell malignant diseases.[27,39,42,43] Furthermore, additional studies may be warranted in previously heavily treated patients if accompanying in vitro studies can be done to confirm or refute the association of a clinical response with in vitro cytotoxicity.

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An AIDS Diagnosis Used as Focus of Malingering

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PSYCHIATRIC DISORDERS are often associated with medical problems or are offered by a patient or physician as an explanation of "medical" symptom complexes.[1,2] A medical evaluation usually and appropriately ensues to explain a patient's symptoms, but a serious consideration of psychiatric diagnoses is often delayed.[3,5] The acquired immunodeficiency syndrome (AIDS) is a new syndrome caused by the human immunodeficiency virus (HIV) and marked by uncommon infections, neoplasms, and other still poorly defined disorders. We present a patient with AIDS who indicated he had symptoms attributable to an organic disease but who ultimately was diagnosed as having a psychiatric disorder in which he was using his AIDS diagnosis to meet other psychosocial needs.

(Levine SS, Helm ML: An AIDS diagnosis used as focus of malingering. West J Med 1988 Mar; 148:337-338)

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ABBREVIATIONS USED IN TEXT

AIDS = acquired immunodeficiency syndrome
CT = computed tomographic
HIV = human immunodeficiency virus
VAMC = Veterans Administration Medical Center

Report of a Case

A 29-year-old homosexual man was admitted to the Denver Veterans Administration Medical Center (VAMC) with new, progressive, left-sided weakness. The patient reported that he had recently moved from Texas where a diagnosis of AIDS had been made. He said he had had numerous opportunistic infections including *Cryptococcus, Pneumocystis,* and cryptosporidiosis. He had received several experimental drugs, including suramin sodium and difluoromethylornithine (DFMO). He brought numerous records with laboratory and diagnostic test results that were positive only for an elevated cytomegalovirus titer. There was no record of an HIV titer.

He reported having increasing left hand weakness about two weeks before admission. Six days before admission, he experienced a stabbing, bilateral temporal headache. He presented to the Denver VAMC six days later. The left-sided weakness had gradually increased to the point of difficulty in holding objects. The headache was accompanied by a brief episode of loss of consciousness. This was followed by nausea, dizziness, confusion and disorientation, and left arm and leg paralysis. The patient also described transient diplopia and a central scotoma.

The patient said he did not have auras, apraxias, incontinence, tonic-clonic movements, drug use, a history of a similar episode, or a history of diabetes mellitus. He had had numerous electroencephalograms in the recent past that were reportedly normal. He had no known allergies and was currently taking no medication. He had attempted suicide in 1984 with an amitriptyline overdose. He had hepatitis in 1976 and genital herpes of an uncertain duration. The patient was an unemployed chauffeur who lost his job after being diagnosed with AIDS. He had a 15-year history of promiscuous homosexual activity. He smoked cigarettes and used alcohol and marijuana occasionally. He said he did not use drugs intravenously.

He was muscular and appeared healthy. There was no fever, his blood pressure was 110/70 mm of mercury, respiratory rate 12 per minute, heart rate 90, weight 93 kg (205 lb), and height 190 cm (6'3"). He had a gold circular earring in his left nipple. The neurologic findings varied with the observer. Cranial nerves I through XII were completely intact except for a weak right sternocleidomastoid muscle. There was a false-positive orbicularis oculi test. Motor strength on the right was normal, but all muscle groups tested in the left upper and lower extremity were weak (0 to 4/5). He was able to stand and walk on both heels and toes. Muscle tone was notably increased in all groups tested with active resistance to movement, relaxed with persistence, and then was normal. A sensory examination showed no abnormalities. Deep tendon reflexes were normal. Cerebellar function was normal except for the left extremities, which could not be tested. He had a leukocyte count of 5,200 per μl with a normal differential, and the sedimentation rate was 11 mm per hour. The platelet count, prothrombin time, and other routine laboratory tests were normal.

Because he was relatively well and because of the inconsistent findings of the examination and laboratory data, we elected to not embark on an emergent diagnostic workup until additional historical information was obtained. A call to the hospital in Texas revealed that his records were lost.

A call to a physician who reportedly knew the patient well yielded a vague history that the patient may have been positive for HIV and that he had diarrhea at one time that resolved and may have been due to cryptosporidiosis. On neurologic consultation, the conclusion was that the symptom complex and history were not consistent with a seizure, migraine, or a typical cerebrovascular accident. The lack of sensory findings was thought to be inconsistent with a hysterical cause. At the request of the neurology service, a computed tomographic (CT) scan and lumbar puncture were done. The CT scan was normal except for a suggestion of mild cerebral atrophy. The spinal fluid was clear; there were three erythrocytes and three leukocytes (all lymphocytes); a cerebrospinal fluid glucose level was 54 mg per dl (serum glucose 80) and protein 29 mg per dl; india ink, acid-fast, and Gram's stains were negative; cryptococcal antigen, VDRL, and cultures were negative.

The patient requested to be put on a status of no resuscitation in the event of cardiopulmonary arrest and to be seen by the psychiatric service. The psychiatrist noted that the patient exaggerated and embellished symptoms, but the psychiatrist did not think the findings could be totally due to fabrication.

The patient's sister was contacted, and she corroborated the AIDS history but gave us no new or additional objective data. On the third day of admission, the neurology service staff obtained some additional history. The patient was living with a woman with left-sided weakness who used a wheelchair to get around. He had also been scheduled to appear in court on the day of admission and was worried about his financial and housing situations. His move from Texas was not precipitated by this illness, as the patient had initially reported, but rather by his being evicted from his home due to his refusal to work. He had worked on a psychiatric service in the past.

The patient was transferred to the neurology service. A magnetic resonance imaging scan and an electroencephalogram were done and were normal. A serum HIV test by the enzyme-linked immunosorbent assay and Western blot methods was positive. The patient was discharged before an interview using thiopental sodium could be done.

Discussion

The differential diagnoses to explain this patient's symptoms include various central nervous system conditions associated with AIDS and three psychiatric disorders—factitious disorder, malingering, and conversion reaction. Factitious disorders and malingering are two disorders in which patients voluntarily control their particular symptom complex. Malingering is usually characterized by a recognizable motivating goal for the presentation. Factitious disorders are characterized by underlying psychopathology where the motivating goal is involuntarily adopted and not recognizable or known to the patient or observers. A diagnosis of malingering should be considered especially for any of the following reasons: there is a medicolegal aspect to the presentation; there is a pronounced discrepancy between the subjective complaints and the objective findings; there is a lack of cooperation; or the patient has an antisocial personality disorder.[6(pp285-290,331-332)]

Conversion reactions, in contrast to the above, are characterized by symptom complexes that are under involuntary control. The physical disorder is apparently an expression of a psychological conflict or need. Symptoms are most often neurologic. Those with conversion reactions often have relief of symptoms with hypnosis, suggestion, or the intravenous administration of barbiturates; this is not the case with malingering.[6(pp244-247)]

This patient was HIV positive but did not have a recognizable pathophysiologic process to explain his symptoms. This was confirmed by extensive consultation and diagnostic evaluations. We became convinced, therefore, that our patient had a psychological disorder. It appears that the physical findings were under voluntary control (malingering or factitious disorder), suggested by the inconsistent findings on examination and the pseudopareses of his cranial nerves. The diagnosis of malingering also is suggested by the recognizable motivating goals: avoiding a court date and a less-than-adequate living situation with notable financial difficulty. A conversion reaction, under involuntary control, might have been even more convincingly ruled out if a thiopental interview had been done.

This patient with an unconfirmed history of AIDS presented with what initially appeared to be a serious symptom complex. It is certainly appropriate to consider the very severe pathophysiologic causes of any such finding in a patient with AIDS. These patients, however, may also acquire psychiatric disorders at least as frequently as other patients or use their AIDS diagnosis for other psychosocial purposes. The increasing number of AIDS patients will continue to face issues of safety, segregation, and prejudice, but the medical profession has the responsibility to diagnose and treat all members of society. A careful clinical evaluation and consideration of the differential diagnosis, including psychiatric disorders, should lead to the correct diagnosis in these patients. A biopsychosocial approach will decrease inappropriate diagnostic testing and improve the outcome for these patients.

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Radiologic Case

Blurred Vision and Headaches in a Patient Positive for HBsAg

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A 57-year-old man presented with the sudden onset of blurred vision and headaches. For four weeks he had had malaise, diffuse joint pains, night sweats, and numbness and tingling of both feet. He was short of breath.

On physical examination he had a blood pressure of 220/110 mm of mercury and signs of congestive heart failure. Pertinent laboratory data included a notably increased erythrocyte sedimentation rate and elevated blood urea nitrogen and creatinine levels. Blood cultures and antinuclear antigens were negative, but his serum was positive for the hepatitis B surface antigen. There was 3+ proteinuria.

After an extensive workup, abdominal angiography was done (Figures 1 and 2).

What are the findings? What is the diagnosis? How would you treat this patient?

SEE FOLLOWING PAGE FOR DIAGNOSIS AND DISCUSSION.

Figure 1.—The photo shows magnification of a selective renal arteriogram. Note several small aneurysms **(arrows)** and irregularity of arteries in the lower pole.

Figure 2.—A selective hepatic angiogram shows aneurysms in hepatic arterial branches **(arrows).**

(Ohmart RH, Cook GC, Paull D, et al: Blurred vision and headaches in a patient positive for HBsAg. West J Med 1988 Mar; 148:339-340)

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ANSWER: Polyarteritis nodosa

The arteriograms show several microaneurysms of the renal (Figure 1) and hepatic (Figure 2) arteries, with irregularity and narrowing. Abnormalities are confined to the medium-sized vessels. Multiple arterial microaneurysms may be produced by trauma, infection, and connective tissue diseases—such as Wegener's granulomatosis—but the number and distribution of aneurysms seen in this patient would be unusual in any of the above cases. The findings, especially in the kidney, are strongly suggestive of polyarteritis nodosa.

Polyarteritis nodosa was first described by Kussmaul and Maier in 1866. The disease involves all three layers of the arterial wall. Early lesions produce necrosis in the media and intima, leading to infiltration of the wall by neutrophils and monocytes. Fibrosis and intimal proliferation follow. Weakness in the arterial wall is responsible for the formation of multiple microaneurysms. Arteries involved with polyarteritis are prone to thrombosis, and this eventually causes ischemia and infarction in the affected organs.

Polyarteritis nodosa varies in extent and severity, from a relatively benign vasculitis to a more severe, often fatal form, affecting the vasculature of many organs. The kidney (80%), heart (70%), gastrointestinal tract (65%), and arteries supplying the peripheral nervous system (50%) are most often involved. The clinical presentation is nonspecific, and no standard symptom complex is seen. Presenting symptoms may include fever of unknown origin, and general malaise and weight loss are common symptoms. Renal failure accompanied by severe hypertension is a result of the vasculitis and is a frequent cause of death. Congestive failure may be due either to the arterial hypertension or to direct involvement of the coronary arteries. Gastrointestinal lesions can give rise to symptoms of "acute abdomen" due to mesenteric ischemia. A bilateral, usually asymmetric, neuropathy is frequently seen, and this is more prominent in the lower extremities.

Our patient has hepatic microaneurysms, an unusual finding in polyarteritis. Involvement of the hepatic arteries only occurs in patients who are seropositive for the hepatitis B surface antigen (HBsAg). This pathophysiology is currently under investigation and may involve immune complex-mediated interactions.

No diagnostic laboratory tests are specific for polyarteritis. The diagnosis is based on the histopathologic finding of a necrotizing vasculitis of small or medium-sized arteries, along with clinical manifestations characteristic of the disease, as described above. In the absence of readily accessible tissue for biopsy, radiographic findings often must suffice in making the diagnosis. The prognosis for untreated patients is poor, with five-year survival rates of approximately 13%. With the use of corticosteroids, five-year survival has improved to 48%. Cyclophosphamide and other immunosuppressive agents have also been used in the treatment of polyarteritis.

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Industrial Accidents—Worker Compensation Laws and the Medical Response

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THE SUBSTITUTION IN 19th-century Europe and America of rapidly moving machinery driven by steam and electricity for hand and water power had the unintended effect of increasing the number of industrial accidents. Efforts to address the impact of this transformation in power included safety appliance acts, factory laws, shop inspectors, minimum-age restrictions, and other self-regulatory and legislative acts designed to give greater protection to workers using high-speed machinery. The workers' compensation laws, exemplary of this new initiative to protect employees, were based on the principle that industrial accidents, except in cases of willful employee negligence, were natural consequences of industrial production, the costs of which should be borne by industry, not individual workers. According to this principle, employers assumed the costs for accidents in the form of insurance premiums; those costs were then passed on to consumers in the price of finished products.

America was slow to accept the idea of workers' compensation, long embodied in European legislation and social policy. Although based on sound economic and ethical principles, this legislation was interpreted by most Americans as infringing on the responsibility of the individual and the freedom of contract for employers. The history of this legislation, including its implementation in early 20th-century America, serves to highlight an important era in labor history and the particular role that the medical profession and individual physicians played in that effort.

European Initiatives

The earliest legislation to support the interests of injured employees was the Prussian Railroad Law of 1838. Substantive changes did not occur until after the formation of the German empire, when the government enacted laws designed to strengthen the social fabric of the nation. The Employer's Liability Law, passed in 1871, gave protection to injured employees working on railroads and in mines, quarries, and factories. Although initially flawed by contradictory language, the act prepared the groundwork for ameliorative legislation that eventually conceded that the "more imperative doctrine of public policy" took precedence over individual or corporate negligence.[1(p573)]

Between 1880 and 1890, Germany expanded its concept of social legislation through a system of compulsory sickness and old age insurance. A tax on the wages of workers supported a fund to protect them during periods of disability from accidents. The extension of the principle of compulsory insurance to disability from sickness occurred without major turmoil within the existing laws. The fund, created out of the contributions of millions of individual workers, produced a sense of security and independence rather than a feeling of dependence on the state.[2(pp70-72)]

The premises on which Germany based its legislation included state control of insurance, the distribution of insurance charges to reduce hardship, the establishment of associations of employers based on the level of accident risk, recognition of employee rights irrespective of the source of negligence, and the establishment of special boards whose jurisdiction remained separate from that of the courts. The insurance system was organized as a bureau within the Department of the Interior. Under its authority were the courts for industrial insurance claims, whose membership included representatives from government, labor, and business and which operated without juries or attorneys representing specific clients. Physician examiners were appointed by the courts to investigate claims made before them. Any payments made by these courts came through the Post Office Savings Bank, which in turn was reimbursed annually by the trade unions. Assessments made by the Post Office Savings Bank were based on statistical records relating to the risk factor in each class of work.[3(pp83-87)]

In England, the first suit for personal injuries was brought in 1837 by a butcher boy against a fellow servant. The case, *Priestly versus Fowler,* established the so-called common employment or fellow servant rule. This rule in common law shifted the burden of responsibility from employers to the shoulders of neglectful fellow servants.[4,5(p173)] In America, Chief Justice Shaw of Massachusetts reaffirmed the fellow-servant rule in the case, *Farnwell versus Boston and Worcester Railroad Company,* of 1842.[2(p38)]

Common-law claims made against employers were usually based on employers' negligence in providing safe working conditions. Although a seemingly reasonable plea, most courts refused to recognize the extended responsibilities owed by manufacturers to employees. Employers, for their part, argued that the negligence was not theirs, that the labor had been contracted for, that the injured plaintiff demonstrated negligence, or that the employee assumed the risk of injury by remaining in employment. Thus, the employees were left to bear the consequences of most injuries.[6(pp57-58)]

Despite the intentions of this judge-made law, high-speed

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machinery and an increased productive capacity made increasingly obsolete the doctrines of assumed risk and contributory negligence. In their place emerged the belief that corporate, public, and even private rights existed for the benefit of the community and that if corporations or manufacturers became public agents, then employees whose disabilities made them and their families a public burden should be entitled to compensation. Moreover, consumers, who benefited from the activity, should bear the cost of the compensation through a charge added to costs of products.

In 1880 William E. Gladstone remedied the interpretive attitude of the English courts by securing passage of the Employer's Liability Act. Modeled after the Prussian Act of 1838, the Gladstone Act abolished the common-law defense but continued to require proof of negligence on the part of either employers or employees. Despite Gladstone's good intentions, employers found it easy to avoid liability by requiring employees to sign contracts renouncing those rights that the act intended to protect.[7(pp15-25)]

England did not fully accept Germany's legislative intent until the Workmen's Compensation Act of 1893, which held that accidents were inherent to industry and unavoidable by either employers or employees. Unfortunately, neither Joseph Chamberlain nor Herbert H. Asquith was able to move the 1893 measure through Parliament that year, mainly because of opposition from manufacturing. Further, the House of Commons refused to accept an amendment inserted by the House of Lords to permit employers to effectively nullify the act by requiring employees to sign contracts renouncing their rights. Not until 1897 did the Workmen's Compensation Act finally pass, bringing protection to nearly 7 million workers in England. Statistics collected following its passage showed that it added little to the cost of the finished product and measurably diminished the litigation incurred by both employees and employers.[7(pp56-86)]

The English compensation laws, although patterned after those in Germany, required no compulsory insurance, relying instead upon "friendly societies" established long before the passage of the Gladstone Act. The intent of the acts was to supplement the existing financial and legal system rather than supplant it with an entirely new program.[6(pp59-60)]

France based the recovery of damages for industrial injuries on the *Code Civile,* which placed the burden of proof upon the employee. An early effort in 1880 by Martin Nadaud to remove the theory of negligence failed in the Chamber of Deputies. In 1883 Felix Faure likewise failed in the Senate to pass an obligatory insurance system for high-risk jobs, which had been based on a similar law in the German Reichstag. Subsequent efforts failed in both chambers in 1888, 1890, 1895, and 1897. In large part, the French legislators were divided on whether the law should be based on removing the principle of negligence, on compulsory insurance, or on the designation of high-risk employment. Not until 1898 did the French legislature pass a law based on *risques professionnels,* which appeared to be less controversial and even less of a burden to employers. Under this new law, each industry assumed responsibility for injuries except those clearly shown to be caused by inexcusable negligence by employees. In cases of total disability, the law awarded employees pensions equivalent to two thirds their salaries. In the event of an employee's death, the law provided dependents with funeral expenses and a pension.[1(p567)]

American Common Law Practice

As in England, the American concept of workers' compensation originated in the common-law rights of individuals. Accordingly, the American system disavowed the doctrine of trade responsibility for industrial accidents and continued to maintain the common-law practice of making compensation dependent on proof of negligence. The law made no guarantee of workers' safety but assumed that most forms of work were associated with some level of risk. In practice, this meant that no compensation was given for injuries sustained as a consequence of "incidental risks" unless an employee could prove that the injuries were "the proximate results of negligence on the part of an employer." In other words, the burden of proof remained with the worker in all instances, a position disavowed by most other industrial nations by 1884.[1(pp704-705)]

In response to claims of negligence, employers had three powerful defenses: first, the injury was due to the contributory negligence of the employee; second, the injury was caused by negligence of a fellow employee; and, third, the risk of injury was understood and assumed by the employee at the time of employment. Also, under common-law practice, employers had to provide reasonable protection to employees and were liable only when their own negligence resulted in injury to a worker. Moreover, employers were entitled to make written, oral, or implied contracts with their employees releasing them from all liability. The assumption of risk taken by employees at the time of employment meant that they waived any right to complain of injuries stemming from their work. Known as "labor's right to get killed," or the "death contract," it precluded employers' responsibility for injury unless they were directly negligent.[1(pp423,707-708)]

The term "contributory negligence" meant that employees who by either omission or commission were the proximate cause of their own injuries were denied compensation. Such was the case of *Martin versus Wabash Railroad,* in which a freight conductor fell from a train while inspecting a hot box. Although investigators blamed the fall on a defective handhold, the court barred the conductor from compensation because it had been his duty to inspect the handholds on all cars. His own negligence removed any liability from the employer.[6(pp12-13,110-111)]

Because employers typically insured themselves against damages brought by injured workers, employees were obliged to fight insurance companies in their efforts to secure compensation. The power of these organizations, equipped with both financial and legal resources, deterred all but the most determined plaintiffs. Estimates suggest that only one employee in eight recovered damages brought against an employer. Moreover, because of legal expenses, less than a third of the monies paid by employers ever reached an employee. As a result, the employers' liability system did little to indemnify the victims of industrial accidents. In large part, the power of insurance companies simply protected employers.[8,9]

Winds of Change

Despite impediments, small but perceptible changes in the common law tempered the harshness of the rulings in cases of personal injury. Ironically, the favoritism long evident in the employers' liability laws served ultimately to undermine public confidence in the results. In 1909, for example, a Con-

necticut commission established to study the plight of industrial workers reported that liability laws were no longer appropriate and recommended some form of compensation law. Public feeling had moved decidedly in favor of fairer treatment for the injured. Incapacitated employees' assumption of full responsibility for their injuries sometimes resulted in a dependency on public funds and public responsibility for dependents, and this led to a demand for a level of compensation more determinable than that in the existing system.[10]

Not too surprisingly, state courts were neither consistent nor compelling in their rulings on personal injury cases. As one critic commented, "The variety and confusion of our state laws and decisions would more than justify Voltaire's comment on the French laws of the eighteenth century—that he had to change laws about as often as his journey obliged him to change horses." Seldom were two courts in accord over definitions, interpretations, amplifications, or modifications of doctrine. The United States Supreme Court noted this fact when it stated, "There is perhaps no matter upon which there is more completely confusing and irreconcilable division in the courts than the one as to what constitutes a test for common service, such as to relieve the master from liability for injury of one servant through negligence of another."[1(pp714,717)]

By the first decade of the 20th century, there emerged a congruence among the American people, their legislative representatives, and the courts that the common-law remedies for personal injuries were ineffective and inequitable under modern industrial conditions. This feeling was best expressed in a report from the Illinois Employers' Liability Commission, which noted that "the present system is unjust, haphazard, inadequate and wasteful, the cause of enormous suffering . . . and of a badly distributed burden upon society."[11]

Employers' liability laws were further eroded by the Federal Employer's Liability Acts of 1906 and 1908, which gave credence to the principle of comparative negligence first enunciated by Justice Breese of Illinois in 1858. Employers could no longer avoid responsibility for grave negligence, even if workers were in some manner negligent. The ruling thus voided the older common-law doctrines of contributory negligence and proximate cause. Within a short period, Maryland (1888), Georgia (1895), Nevada (1905), Florida (1906), Nebraska (1907), North Dakota (1907), South Dakota (1907), and Wisconsin (1907) had incorporated the principle of comparative negligence into law.[1(p712)]

TABLE 1.—*Enactment of Original Compensation Laws*

Year	No. of Laws Enacted	Total No. of Laws	Jurisdictions
1908	1	1	United States
1911	10	11	California, Illinois, Kansas, Massachusetts, Nevada, New Hampshire, New Jersey, Ohio, Washington, Wisconsin
1912	3	14	Arizona, Michigan, Rhode Island
1913	8	22	Connecticut, Iowa, Minnesota, Nebraska, New York, Oregon, Texas, West Virginia
1914	2	24	Louisiana, Maryland
1915	10	34	Alaska, Colorado, Hawaii, Indiana, Maine, Montana, Oklahoma, Pennsylvania, Vermont, Wyoming
1916	2	36	Kentucky, Puerto Rico
1917	5	41	Delaware, Idaho, New Mexico, South Dakota, Utah
1918	1	42	Virginia
1919	3	45	Alabama, North Dakota, Tennessee
1920	1	46	Georgia

In the years following 1909, states enacted laws that made it possible for employees to recover compensation for injuries arising from industrial accidents (Table 1). In the most liberal of these laws, states did away with the fellow servant rule, restricted the interpretation of assumed risk, and insisted on some level of compensatory damages regardless of an employee's contributory negligence.[10(p57)]

One obstacle to reform was the claim that unless legal regulations uniformly affected all within a particular industry, single-state legislation would create a competitive advantage for companies refusing to invest in a safer environment. Such was the position of match manufacturers, for instance, most of whom recognized the dangers of "phossy jaw" poison that affected many of their employees in the manufacturing of the phosphorus match. In testimony before Congress, however, match manufacturers stated that they were unwilling to substitute a safer compound unless the law in all states required them to do so.[12] To compensate for this tendency, the Conference of Commissioners on Uniform State Law meeting in New York sought the enactment of uniform compensation laws among the industrial states to remove potential obstacles created by single-state legislation.[10(p60)]

Legislative Beginnings

As with much social legislation, the people of the United States began somewhat tardily to educate themselves on workers' compensation. The earliest report published in America was John Graham Brooks's *Compulsory Insurance in Germany* (1893), and the earliest state commissions appointed to study the problem were in 1909 in New York, Wisconsin, and Minnesota.[13] These studies concluded that the existing employers' liability system founded on common law was inadequate, wasteful, and "wholly unsuited to the present industrial conditions."[14]

Early efforts in New York in 1898, Maryland in 1902, Massachusetts in 1908, and Montana in 1909 to pass workers' compensation acts proved unsuccessful; these acts were either declared unconstitutional or limited in scope because they were voluntary. In 1910 local funds were created by the state of Maryland for the protection of coal and clay miners in Allegheny and Garrett counties. Within two years, commissions and legislatures had prepared compensation bills in the states of Massachusetts, Ohio, Minnesota, Illinois, Wisconsin, New Jersey, Missouri, Washington, Pennsylvania, and West Virginia. In addition to state commissions, the Conference of Governors, the Conference of Uniform State Law Commissioners, and the American Bar Association established committees to review the subject, as did the American Association for Labor Legislation, the American Civic Federation, and the National Association for Manufacturers. In the nation's capital, President Taft appointed a federal commission to review the need to compensate workers involved in interstate commerce. The result was a federal act that, while limited in application and benefits, became the first real workers' compensation act adopted in the United States.[10(pp56,59)]

A physician, W. H. Allport, MD, writing in 1909, blamed America's tardiness in providing workers' compensation on the republican form of government that operated through compromise or consensus legislation rather than radical or systemic change. He attributed this behavior to Americans' worship of common law and fear that any change in its essential nature would have a deleterious effect on national values. Allport also accused the courts of unnecessarily hindering progress by their fear of legislative encroachment beyond the limitations imposed by the Constitution. Finally, he noted that jurisdiction between federal and state rights created an inevitable obstacle to any far-reaching solution to industrial legislation.[1(p706)]

Reflecting the reform-mindedness of the era's Progressives, Allport urged the creation of a "small but compact and representative party" independent of the two-party structure to initiate the needed legislation in America. In his enthusiasm, he reflected his admiration of the Social Democrats in Germany and their ability to remain apart from the Conservative, Liberal, and Clerical parties. He also recommended the establishment of bureaus to monitor and publish statistical data on the workplace. Existing bureaus maintained by the federal government and the state governments of Wisconsin, Massachusetts, and New York exemplified the type of reporting essential for effective legislation. Finally, Allport encouraged the states and the nation to produce lawmakers "disinterested enough to escape local and corporate influence, and skillful enough in the practice of legislative technic to frame a series of valid measures which will adequately meet the present situation."[1(p718)]

Medical Response to Compensation Laws

With the advent of compensation laws, major changes occurred in the physician-patient relationship and in the interrelation of physicians, employers, insurance carriers, and compensation boards. Clearly, physicians became a critical element, standing as medical referees whose examination was mandatory in cases brought before compensation boards. The physicians' role was to determine the extent or duration of a disability and all facts germane to the amount of an award.[15]

Under the new state compensation laws, physicians faced increased demands on their expertise, including injured workers' recourse to additional consultations. Hospital reports and bills, discharge certificates, letters, and other written and oral communications became formidable new responsibilities for physicians.[16] Commissions demanded radiographs and tests and "the surgeon [was] waking up to the fact that he must be more careful in making his reports, that he is not alone in the watching of the results of his work." No longer could incompetent physicians "do a careless or indifferent piece of work"; their reports now came under the scrutiny of the chief medical examiner of a commission or board and by other physicians if deemed necessary.[4]

Under the new legislation, physicians were expected to maintain intact the integrity of their confidential relationship with patients. In no case were physicians to serve as informers for employers or to betray the confidences of injured employees. While the law prevented physicians from testifying against their patients, it did modify this dictum by requiring a physician to testify when so ordered by a commission or board. As one former chair of the Wisconsin Industrial Commission noted, "The doctor should faithfully maintain his fidelity to his patient until required to give evidence by the commission, and then to volunteer nothing that in his judgment would be unethical without submitting to the commission's ruling." Despite this caveat, physicians on annual retainers or those whose practices derived solely or largely from contract work sometimes abused this confidence.[17]

The legislation made available several forms of medical delivery systems. In "contract services," the state employed a specified number of full-time physicians to treat injured workers. This method, used by both the Army and Navy, proved workable in the larger cities but too costly in the smaller towns. Established physicians objected to the contract system because it did "not attract the highest class of practitioners." It also became the source of considerable friction between state-employed surgeons and the medical societies. The profession also opposed a variation of the contract system based on per capita per annum. This system, originating first among the lodges in New York and other large cities, allowed

Dear Sir:

For many years we have had a yearly arrangement or contract with Dr. _____ for full surgical treatment of the employees of these concerns insured by us in _____. There was no legal obligation on our part to provide that service, but from motives of policy, considering not only the unfortunate condition of the employees, but the convenience of the employer, we adopted that plan. It has now become a LEGAL obligation of the employer to furnish such service as above. We are considering the cancellation of existing contracts and adopting a Fee-bill which two or more physicians in _____ will agree to. Your name has been mentioned by one or more of the mills which we insure. We should be glad to have from you any suggestion regarding a reasonable Fee-bill. The table should be made with some reference to the ability of the employer to pay for such service. This has been the decision of the Massachusetts Industrial Accident Board, which no doubt will be followed by the Courts in Rhode Island. If you can agree on a Fee-table, we should desire to have a further understanding with any physician whose services we shall furnish on behalf of the insured employer that he be not over-solicitous for his patient, giving him only such attendance as the case actually and reasonably may require.

Figure 1.—The letter shown was mailed to selected members of the Massachusetts Medical Society (from Rogers[19]).

physicians to bid on contracts, which resulted in an unusually low per capita payment.[14,18]

Typical of the contract system was the letter received by a member of the Massachusetts Medical Society (Figure 1). The letter clearly implied that the lowest bidder would obtain the work regardless of qualifications.

A second plan, known as "unlimited choice," gave employees the privilege of choosing any physician. Although both physicians and patients liked this plan, it sometimes led to patients choosing physicians who would "magnify the injuries and thus increase the period of disability and enlarge the award." A third type of medical care, known as "limited choice," gave workers a choice of physicians from an approved list. Although the system was disliked for its restrictiveness, it eliminated many of the abuses common in the unlimited system. Specifically, it reduced the market for quacks and charlatans and, ultimately, reduced the cost to the state. The compensation laws compelled employees to accept the physician that an employer chose to use. When an employee decided on a physician or hospital other than that offered by the employer, the cost fell to the employee.[18]

Some physicians supported the state compensation laws because the law insured payments for their services. Within the bureaucracy created to sustain the legislation, however, physicians found that they were no longer free agents. For one thing, both employers and commissions preferred greater standardization of medical services and stabilization of fees. In practice, this meant the creation of fee schedules or fee bills, contract surgical procedures, and the designation of specific hospitals (Table 2).[19,20]

The Fee Bill

Without question, the fee-bill issue became "the greatest bone of contention" between the medical profession and the states that formulated compensation acts. In Massachusetts, California, Ohio, and Michigan, commissions based their fee

TABLE 2.—*Insurance Company Fee Table for Surgeons, 1915**

Service	*First Aid, $*	*Subsequent Aid, $*
Ordinary day visit, not necessitating antiseptic dressing	1.50	1.50
Visit necessitating and including antiseptic dressing	2.00	1.50
Visit including both antiseptic dressing and necessary operative procedures in ordinary cases of contusion, lacerations, incisions, punctures and the like	2.00-5.00	1.50
Night visit—9 PM to 7 AM	2.50	
Office examination and report, ordinary	1.00-2.00	
First attention at office, including operative procedure and dressing of ordinary wound	1.00-2.00	1.00
Removal of foreign body from conjunctiva	1.00-2.00	1.00
Removal of foreign body from cornea	2.00	1.00
Amputations		
Hip joint	10.00	2.00
Thigh at any point	50.00	2.00
Leg or foot	25.00	2.00
Shoulder joint	50.00	2.00
Arm or forearm or hand	25.00	2.00
Metatarsal or metacarpal joint, single	15.00	1.50
Two or more	20.00	1.50
Finger or toe, single	10.00	1.50
Two or more	15.00	1.50

Fractures	*First Aid, $*	*Subsequent Aid*	
		Hospital or Home, $	*Office, $*
Upper arm	15.00	1.50	1.00
Forearm, one bone	15.00	1.50	1.00
Forearm, both bones	20.00		
Femur	40.00	1.50	1.00
Lower leg, one bone	15.00	1.50	1.00
Lower leg, both bones	15.00-20.00	1.50	1.00
Jaw	10.00	1.50	1.00
Ribs, one or more	5.00	1.50	1.00
Patella	25.00	1.50	1.00
Pelvis	15.00	1.50	1.00
Metatarsal or metacarpal joint	5.00	1.50	1.00
Finger or toe	5.00	1.50	1.00
Two or more	5.00	1.50	1.00
Scapula	15.00	1.50	1.00
Clavicle, full aid	15.00	1.50	1.00
Nasal bones	5.00	1.50	1.00
Compound fractures, add 25% for first aid only			

*From Rogers.[19]

(Continued on Next Page)

bills on a yearly income of $600 or less, reasoning that under the older employers' liability laws, many workers would have been treated without charge. Under the compensation acts, however, physicians were virtually assured of payment for their services. Thus, when the House of Delegates of the New York State Medical Society created a committee to consider the matter of fee schedules, the committee reported that the fee bills in the various states were similar to one another and that the schedule of prices was "comparatively satisfactory."[20]

Five members of a special committee appointed by the New York State Medical Society assisted in developing the fee bill adopted by the Workmen's Compensation Commission in New York. Despite this cooperation, certain physicians challenged the authority of the special committee to enter into any contract with the commission. They accused the committee of violating its charge to present the views of the profession on questions that might come before the compensation committee. According to Henry Stark, MD, in remarks made before a county medical society in 1915, "the committee was not authorized to fix a scale of prices with the commission; its duty was first to report back to the House of Delegates which created it." Worse, the state medical society represented less than half of the medical profession in the state; the remainder had never been consulted on the issue. "We do not object to the new law," commented Stark. "We recognize it has come to stay, but we want fair treatment from those who are empowered to regulate and prescribe fees for services rendered."[21]

Medical opponents were particularly upset over the re-

(Continued from Previous Page)

TABLE 2.—*Insurance Company Fee Table for Surgeons, 1915**

Dislocations and Other Services	*First Aid, $*	*Subsequent Aid*	
		Home Visit, $	*Office, $*
Shoulder	10.00	1.50	1.00
Elbow	10.00	1.50	1.00
Hip	20.00	1.50	1.00
Knee	10.00	1.50	1.00
Ankle	10.00	1.50	1.00
Wrist	5.00	1.50	1.00
Finger	2.00	1.50	1.00
Jaw	5.00	1.50	1.00
Trephining skull	50.00	1.50	1.00
Ligating important arteries	10.00	1.50	1.00
Reduction of ordinary hernia when due solely to recent injury, and applying truss	5.00	1.50	1.00
Reduction of strangulated hernia by taxis	10.00	1.50	1.00
Herniotomy	50.00	1.50	1.00
Enucleation of eye ball	25.00	1.50	1.00
General anesthetic	5.00		
Complete physical examination with report	3.00-5.00		
Autopsy—complete with written report	50.00		
Attending, but not performing	10.00		
Testimony in court as to simple fact of injury	10.00		
Expert testimony	15.00-25.00		
Passing catheter	2.00		
X-ray (to be taken only on orders by the company)	2.50	each for first two pictures	
X-ray (to be taken only on orders by the company)	2.00	each for subsequent pictures	

Some Other Contested Charges	*Charged, $*	*Allowed, $*
Laceration of flexor tendons of forearm with compound fracture of carpus, charges for tendon suture, ether, assistance, and 2 weeks' treatment	80.00	61.00
Radical operation for hernia	100.00	35.00-50.00
Fracture of arm	25.00	15.00
Contusions following automobile accident at some distance	15.00	5.00
Subsequent office dressing	1.00	.50
Laceration of finger, first aid	5.00	3.00
Subsequent dressings	2.00	1.00
Septic hand, three operations, with ether, assistance, and subsequent treatment	94.00	61.00
Fractured ribs	15.00	5.00
Incised wound of hand	5.00	2.00
X-ray photograph	10.00	5.00
Cellulitis following lacerated wound, 2 operations under ether, 2 and 3 visits a day	125.00	40.00
Colles' fracture	25.00	10.00
Foreign body cornea	10.00	2.00
Enucleation of eye	75.00	50.00
Cut of leg, sewing extensor tendons	10.00	2.00
Fracture of both bones of leg, unsuccessful previous attempt at reduction, operation, and special appliances	250.00	50.00

*From Rogers.[19]

fusal of insurance companies to honor bills in excess of the published schedules. Journal articles in the early 20th century contained numerous examples of correspondence between physicians and companies that challenged bills considered suspiciously large, lacking sufficient supporting documentation, or in excess of standard fees. Companies encouraged fee bills on the grounds that while they amounted to a discount from local rates, physicians did not suffer a loss from bad debts as they frequently did in private practice. Companies argued that they paid their bills and made up for the discount by supplying a much larger volume of business to physicians.[19]

Despite claims that physicians did not benefit from the compensation acts, evidence indicates that remuneration increased four to five times what it had been under the older employers' liability insurance system. Many physicians had to wait for fees under that system or, worse, go without.[20]

The Specter of Socialism

Although legislatures in 24 states had passed compensation laws by 1915, the average physician had "little or no knowledge of the basis and principles of this type of insurance." According to A. C. Burnham, MD, of New York, few physicians really comprehended the idea of social medical insurance. Specifically, they had lost sight of the fact that they were working for the state.[18] When many of these physicians did learn of the law and its implications, they objected to the authority it gave to the state "to barter for our service as though it were a piece of merchandise or a real estate parcel." The response of many physicians to the compensation laws resembled a form of jingoism that viewed the legislation as a threat to American values.[21]

Opponents of the compensation laws included physicians who viewed the legislation as "the great effort which the majority is making to socialize the [medical] profession." Charles A. E. Codman, MD, of Philadelphia took particular exception to social legislation, observing that the establishment of public parks, municipal piers and hospitals, transit systems, and the Interstate Commerce Commission were all evidence of the government's intent to extend socialistic doctrines throughout American society. He interpreted the workers' compensation laws as the first step to socialized medicine.[22]

In Illinois, physicians sided with industrial management, claiming that socialistic ideas were behind the compensation acts and fearing that corporate wealth would no longer be protected under the law. H. C. Fairbrother, MD, District Surgeon for the Illinois Central Railroad, accused workers of being influenced by ideas wholly alien to their best interests. To fight this "evil teaching," Fairbrother sought legislation that would establish a new system of education. Like many in the days of America's so-called Progressive Era, Fairbrother disliked any emphasis or interpretation of life as class struggle, believing that social upheaval was no way to bring about a better society. Although he desired change, he found it difficult to advocate anything that would result in changing the existing structure of society.[16]

Speaking for the Illinois State Medical Society in 1920, W. F. Grinstead, MD, president of the society, condemned the compensation acts as a blight brought to America from England and Germany that was now creating a "most staggering blow to the efficiency of the healing art as well as the greatest humiliation to the medical profession that the present and last centuries have administered." Like others before him, he identified the legislation as a "species of socialism" that menaced the nation's health by unjustly and greedily exploiting the medical profession through the machinations of accident insurance companies. Grinstead refused to sign fee bills prepared and submitted by insurance companies, declaring as unacceptable any service provided at "cut rate, not to say a starvation rate." In particular, he resented the multitude of forms required by the company unless he was paid for the time and labor needed to fill them out. Companies made money by driving hard bargains with individual members of the medical profession. The result was that "the doctor must go hungry, a victim of greed."[23]

Understandably, medical societies showed increasing interest in the experiences of European nations with compensation legislation. In 1914, for example, Edward F. McSweeney, a member of the Industrial Accident Insurance Board, spoke before a packed meeting of the Massachusetts Medico-Legal Society to compare the English system of compensation with that of the United States. He concluded that "in some way the national character has been undermined by the attempt to substitute the beneficence of the state for the individual ambition and farsightedness of the man himself."[24]

Conclusion

In the years preceding the compensation laws, medical opinion differed little from that of American mainstream; physicians exhibited no especially coherent social philosophy regarding industrial accidents. Like other representative groups, medical opinion could not be squeezed into any one intellectual mold. Instead, physicians exhibited a potpourri of ideas and attitudes ranging from rugged individualism and nostalgia for a simpler life to a suspicion of European ideas and an iconoclastic attack on the social system. By 1910, however, the American middle class had moved toward cautious reform, calling for strong leadership, big government, regulation in the public trust, and more scientific expertise and management. Physicians shared in this new, progressive flavor in American politics, and many found a distinct sympathy for Theodore Roosevelt's penchant for "bully politics" and civic responsibility toward labor and the poor. The workers' compensation laws became a reflection of that new attitude.

Nevertheless, many physicians misunderstood the impact that workers' compensation legislation would ultimately have on their individual practices and on their socioeconomic status, as well. For one thing, they found themselves weakened by and nervously critical of the legislation's more intrusive aspects. Not content to simply debate the issue, physicians and their medical societies soon agitated against what they perceived to be a radical reconstruction of society. By the 1920s, the medical profession had become divided—albeit unevenly—between the remnants of the earlier Progressives who continued to teach the efficacy of moral suasion and social justice and an increasingly conservative group who were more concerned with economic security and free competition. With minor modification, the elements of this schism would continue to harden as the nation approached the watershed years of the Great Depression.

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Book Review

The Western Journal of Medicine *does not review all books sent by publishers, although information about new books received is printed elsewhere in the journal as space permits. Prices quoted are those given by the publishers.*

Arterial Anatomy of Skin Flaps

George C. Cormack, MA, MB, ChB, FRCS(Ed), formerly Department of Anatomy, University of Cambridge, and Fellow of Queens' College, Cambridge, and B. George H. Lamberty, MA, MB, BChir, FRCS, Consultant Plastic Surgeon, Addenbrooke's Hospital, Cambridge, and Associate Lecturer, University of Cambridge. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1987. 442 pages, $195.

This is a truly elegant compendium—an exhaustive reference encompassing history, anatomy, application, and detail. It exhibits the ingredients necessary for the competent selection and design of cutaneous, fasciocutaneous, and musculocutaneous flaps to cover defects anywhere on the human body.

The work embodies detailed line drawings of the design of almost every flap extant. There are abundant references for further research on method and application. A compilation and expansion of the work of Manchot and other students of the circulation of the skin is elegantly displayed. The radiographic studies of surface circulation are superbly done and are an exemplary testimonial to the brilliant and gargantuan effort (and incumbent sacrifice) of the authors.

The book starts with descriptive chapters generally discussing microcirculation and then, more specifically, the circulatory systems: cutaneous, musculocutaneous, and fasciocutaneous. These discussions include theoretical, experimental, and actual methods to alter or enhance circulation by pharmacologic or surgical delay or design.

There follows a major section on blood supply, by regions of the body, to introduce the largest section of the book, which discusses in detail the planning of flaps by regions.

The title of the book is misleading in that it does not convey the presence of the eminently useful physiologic, pharmacologic, and clinical material contained.

This remarkable book is an unusually worthwhile contribution that should be, not in the library, but on the desk or at the bedside of anyone who presumes to reconstruct the human surface.

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Family Planning Among Southeast Asian Refugees

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Five different Southeast Asian groups were studied to document family planning knowledge, attitudes, and practices, and to identify current barriers to care. Significant differences exist among ethnic groups in their knowledge and use of effective methods of contraception, as well as variations in the timing of when to adopt family planning practices and in the preferred number of children. Nearly 70% of the sample had experienced barriers to services, including language, transportation, and a lack of awareness of available services.

(Minkler DH, Korenbrot C, Brindis C: Family planning among Southeast Asian refugees. West J Med 1988 Mar; 148:349-354)

As of September 1986, the influx of Southeast Asian refugees into the United States following the fall of South Vietnam in 1975 had reached 806,000 persons.[1] While these refugees share certain common problems of resettlement with other groups of refugees, immigrants, and undocumented aliens, nevertheless, they have unique characteristics. The impacts of war, involuntary dislocation, family separation, the deaths of children and relatives, and, in many cases, prolonged detention in refugee camps have all added to the problems they face in their attempt to become self-sufficient in a new and unfamiliar environment.

Although data regarding fertility and family planning practices in the countries of origin of these refugees are limited, local surveys in the region indicate fertility substantially higher than in the United States.[2,3] Likewise, studies of fertility of Southeast Asian refugees in the United States are few compared with those addressing their health status, though persistently high fertility following immigration is documented in a few studies.[3-6]

Our study was designed to elucidate the variations in knowledge, attitudes, and practices and the barriers to service affecting the family planning behavior of Southeast Asian refugees, many of whom have resettled in or secondarily migrated to California. The purpose of this research is to assist policymakers, planners, and service providers in reducing barriers to the access and use of services for this unique population facing the challenge of acculturation. We address primarily the problems of the second wave of refugees—those entering from 1980 onward—many of whom have been less successful in achieving self-sufficiency than their first-wave predecessors.

Population and Methods

Sample

Structured in-depth interviews (N = 438) were conducted among ever-married Vietnamese, Cambodian, lowland Laotian, Lao Mien, and Lao Hmong refugee men (N = 210) and women (N = 228) of reproductive age (15 to 44 years for women, 15 years and older for men) who were residents of Alameda, San Francisco, and Santa Clara counties.

A sample of convenience was necessitated because the confidentiality of general lists of refugees made it impossible to select participants randomly. Moreover, these refugees were particularly sensitive to any idea of being contacted through a government agency. Thus, the convenience sampling procedure was judged to be the cross-culturally sensitive approach to studying contraceptive behavior in a sexually active group of refugees. Potential respondents were approached by interviewers during visits to refugee screening clinics, other health clinics serving refugees, and social service agency locations. After the nature of the research project was explained and confidentiality assured, appointments were arranged to conduct the interviews in a convenient and comfortable setting for the participants, usually their homes. The interviewer's sex was the same as that of the interviewed. In those instances in which the number of respondents was inadequate, the "snowball" sampling procedure was implemented: refugees interviewed were asked to provide names of other members of their communities who might agree to be interviewed. Locating Hmong respondents was particularly difficult, but a Hmong community existed in Contra Costa County (California), and the study area was expanded to include this population.

Overall, 10% of 485 persons—and 25% of the Hmong—declined to participate. The most common reasons for refusal were a lack of time or a hesitancy to having an interview in their home that could not be dispelled by offering other locations, and, among the Hmong, shyness in discussing the topic of family planning.

Lowland Laotians formed the greatest portion of the sample (29%), followed by Cambodians (25%), Vietnamese (21%), Lao Mien (13%), and Lao Hmong (11%). Together, Laotians from lowlands and highlands comprised 53% of the sample. The proportions of men (48%) and women (52%) were not statistically different ($P < .05$), nor were they different for any of the ethnic groups except the Lao Hmong (P

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This study was supported by a grant from the Office of Population Affairs of the United States Department of Health and Human Services and conducted in collaboration with refugee health screening agencies in Alameda, San Francisco, and Santa Clara counties.

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< .01). Because it was difficult to get the Hmong women to participate, twice as many men (7%) as women (3%) were interviewed.

Respondents differed in background, with about a third each from rural areas (40%), towns (29%), and cities of more than 25,000 people (31%). The Mien and Hmong, however, were almost entirely from villages and towns; lowland Laotians and Vietnamese were predominantly from towns and cities. Only the Cambodians were evenly distributed in their geographic background.

More than half of those interviewed had entered the United States within two years of the interview (25% in 1983 and 28% in 1984). This selection of recent refugees of reproductive age was the only screening of possible respondents that was done. The selection was done to reduce the likelihood that knowledge, attitudes, and practices of family planning had been affected by experiences in the US. Second-wave refugees—those arriving since 1980—composed 80% of the sample. Almost all of the refugees (95%) had been in refugee camps, more than 39% of them for two or more years.

Clinic records had indicated that Southeast Asians rarely reported any premarital or extramarital sexual activity, and the sample for in-depth interviews, therefore, was restricted to married persons living with their spouses or divorced, separated, and widowed persons. Only 5% of this sample was not currently living with a spouse. Only one member of a couple was included.

Significantly more women (20%) than men (12%) reported never having had any schooling ($P < .001$). For those women who had had any schooling, however, the proportion with one to six years of schooling (22%) was not different from that for men (21%, $P < .05$). Most Lao Mien and Lao Hmong refugees had had no schooling (88% and 62%, respectively); this finding was significantly different from that in the other groups ($P < .0001$). The Vietnamese had the highest rates of schooling, with only 3% having had no schooling ($P < .001$) and 17% having had more than 12 years of school. The Cambodians and lowland Laotians had levels of education in between the other ethnic groups (24% and 23%, respectively, had had no schooling).

In 86% of cases neither the respondent nor the spouse was employed. About half the sample reported earning from $500 to $1,000 per month (53%), but most of the rest (43%) earned from zero to $500 per month. Nearly 90% were receiving some form of public assistance, either through cash grants, Medicaid, supplementary security income (SSI), or food stamps.

Interview

Interviews were conducted by trained bilingual and bicultural interviewers matched with respondents by ethnicity, language, and gender. Interviewers were selected from refugee health screening clinics, mutual assistance agencies within the ethnic communities, volunteer agencies, and leaders of refugee groups in the three counties. Because of the delicacy of so intimate a topic as family planning, care was taken to make interviewees as comfortable as possible. No remuneration was offered because the Southeast Asian community advisory board and health workers indicated this practice would actually increase suspicion of the purposes of the survey. In spite of many precautions, some limitations on the completeness and accuracy of data must be assumed, especially a bias to stereotyped responses.

Interview materials, both questionnaires and an informed consent form, were pretested by interviewers and research team members. The final questionnaire containing closed and open questions was translated into Vietnamese, Cambodian, and Lao and then translated back again into English by different translators to insure accuracy. Items that were distorted by retranslation were clarified and reworded. The Hmong translation was done by the Hmong interviewers (one man, one woman) but not verified.

Data Processing

Most questions were in the short answer format with multiple choices provided. Open-ended responses were coded by two independent raters using content analysis of responses. After discordant codes were reconciled by a third rater, all response codes were key entered. Double entry was used to verify the accuracy of all entries. The Statistical Analysis System (SAS) (version 82.3) was used for editing. Checks on consistency of the respondents' answers with repetition of the same question at different times in the survey indicated that consistency on family planning questions was about 93%. Missing data varied greatly among questions, and, in general, variables with better than 97% response rates were used.

Continuous variables were compared using t tests after testing for the normalcy of their distribution. Discontinuous variables were analyzed using χ^2 analyses. Other nonparametric analyses were done on the ranks of certain variables indicated in the results. All data were analyzed with the SAS software (version 82.3) on an IBM 3370 mainframe computer.

Results

Preferred Family Size

The participants were asked, "In your homeland, what is the best number of children to have?"* The results are shown in Table 1. Of the 438 refugees, 19 did not answer this question. The number preferred varied greatly with the ethnic group. The highest number—9.0 ± 0.5 standard error of the mean (SEM)—was indicated by the Hmong. The Vietnamese indicated a significantly lower number—3.2 ± 0.2 SEM—than any other group ($P < .0001$). The significance of these differences in ethnic groups persisted after analysis that controlled for sex and rural background of the respondents.

*While the same question was asked of the respondents ". . . now that they were in the United States," the large percentage of people answering zero or one child indicated that some had answered the question, "How many more children were best to have in the United States?" while others answered, "How many total children were best?" Thus, the results were uninterpretable.

TABLE 1.—*Preferred Number of Children to Have by Ethnicity and Gender*†

Ethnicity	Men N	Men	Women N	Women	Both N	Both
Cambodian . . .	53	4.5±0.2	58	5.7±0.2	111	5.1±0.2
Lao Hmong . .	30	8.1±0.5	13	11.5±1.2	43	9.0±0.5‡
Vietnamese . .	42	3.2±0.2	48	3.2±0.2	90	3.2±0.2§
Lowland Laotian	52	5.4±0.4	66	4.2±0.2	118	4.7±0.2
Lao Mien	23	5.1±0.3	34	6.5±0.2	57	5.9±0.2
Total	200	5.1±0.2	219	5.1±0.2	419	5.1±0.1

*Mean ± standard error of the mean.

†Question asked was, "In your homeland, what is the best number of children to have?" Of the 438 participants, 19 did not answer this question.

‡Significantly higher than any other group at the $P < .0001$ level.

§Significantly lower than any other group at the $P < .0001$ level.

The preferred number of children to have in the homeland was higher for those respondents from village backgrounds (6.0 ± 0.02) than for town respondents (4.5 ± 0.2; $P < .0001$). The ideal number of children was highest for village women (7.0 ± 0.4), who were the only geographic group in which women preferred more children than the men from the same geographic background ($P < .0001$).

Preferred Family Composition

All ethnic groups expressed a preference for a greater number of boys than girls ($P < .05$; Table 2). Although the Vietnamese preferred the smallest number of boys and girls, the statistical difference between the boys and girls was strongest in this group ($P < .001$). While there was no significant difference between men and women when asked the best number of boys and girls to have, in respondents with a rural background, there were distinct preferences for boys. Those who had lived in cities also expressed a significant preference for boys—2.5 ± 0.2 SEM compared with 2.2 ± 0.1 SEM for girls; $P < .05$.

TABLE 2.—*Preferred Number of Boy and Girl Children to Have by Ethnicity**†

Ethnicity	*No.*	*Boys*	*Girls*	*Ratio of Boys/Girls*
Cambodian	111	2.7±0.1	2.4±0.1‡	1.1
Lao Hmong	37	4.7±0.3	3.9±0.3‡	1.2
Vietnamese	89	1.8±0.1	1.5±0.1§	1.2
Lowland Laotian	118	2.5±0.1	2.3±0.1‖	1.1
Lao Mien	57	3.1±0.1	2.8±0.1‡	1.1
Total	412	2.7±0.1	2.4±0.1‡	1.1

*Mean ± standard error of the mean.
†Question asked was, "In your homeland, what is the best number of children to have? How many boys? How many girls?" Seven people who answered the question in Table 1 did not answer this question.
‡Significantly less than best number of boys at the $P < .01$ level.
§Significantly less than best number of boys at the $P < .001$ level.
‖Significantly less than best number of boys at the $P < .05$ level.

Family Growth Rate

The pregnancy histories revealed that in general few refugees had not started families at ages younger than 20 years. The median age at first pregnancy was 21. When respondents were asked the best age for a woman to start having children, the median value was 20 years of age: 36% said 20 years of age, 36% said younger than 20 years of age, and 28% said older than 20 years.

Women older than 40 years had had an average of six pregnancies and four births (Figure 1). The differences represent losses due to spontaneous and induced abortions and stillbirths. After correcting for a 6% reported rate of induced abortions, fetal death rates appear to be as high as 44 per

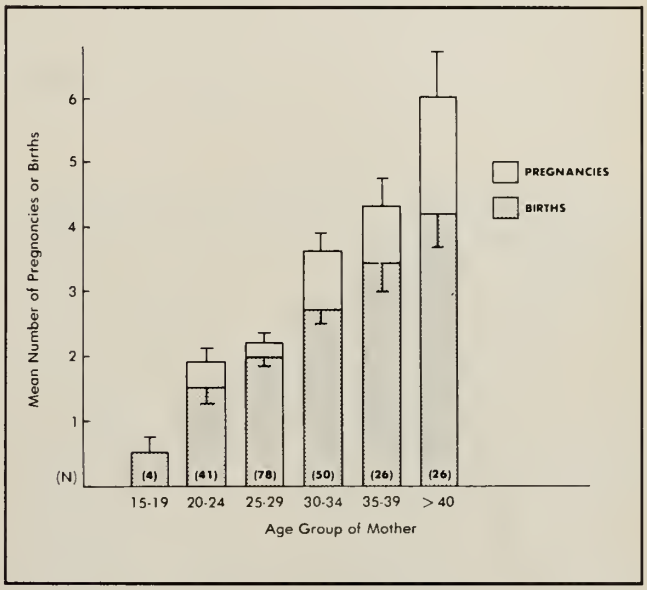

Figure 1.—Mean number (± standard error of the mean) of pregnancies and births for Southeast Asian mothers of different ages.

TABLE 3.—*Awareness of Specific Family Planning Methods Ranked by Ethnic Group*

		Cambodians		*Lao Hmong*		*Vietnamese*		*Lowland Laotian*		*Laotian Mien*		*Average Overall Rank*
Family Planning Methods	*No.*	*Percent*	*Rank*	*Percent*	*Rank*	*Percent*	*Rank*	*Percent*	*Rank*	*Percent*	*Rank*	
More Effective Methods												
Oral contraceptives	298*	93	4.0	73	1	91	1	75	2.0	100	1	1.8
Female sterilization	329	94	3.0	46	2	86	4	79	1.0	95	3	2.5
Intrauterine device	289	77	6.0	31	5	90	3	70	4.0	80	5	4.6
Male sterilization	285	87	5.0	28	6	83	5	67	5.0	67	6	5.4
Injectable	270	94	2.0	26	7	43	10	65	6.0	97	2	5.4
Subtotal	370	96	..	51	..	96	..	84	..	100	..	..
Other Methods												
Condom	325	95	1.0	45	3	91	2	71	3.0	93	4	2.6
Fertility awareness (rhythm)	193	38	7.0	21	8	82	6	44	7.0	46	8	7.3
Foam	131	20	9.0	11	10	37	11	43	8.5	54	7	9.1
Abstinence	114	18	10.5	39	4	43	9	41	10.0	5	14	9.5
Withdrawal	136†	24	8.0	3	12	71	7	30	13.0	29	11	10.2
Douche	110	18	10.5	0	14	45	8	34	11.0	29	10	10.7
Diaphragm	87	9	12.0	11	9	27	12	32	12.0	33	9	10.8
Suppository	78	6	14.0	3	13	26	13	43	8.5	12	13	12.3
Jelly	69	6	13.0	8	11	24	14	24	14.0	27	12	12.8
Subtotal	347	97	..	49	..	95	..	76	..	96	..	..
Total	399	97	..	53	..	99	..	86	..	100	..	..

*Although the number is smaller than that for female sterilization or the intrauterine device, the proportion is greater because one group of respondents (N=20) was not asked about oral contraceptives; 19 reported that they were not aware of any family planning methods.
†Although the number is greater than that for abstinence or foam, the rank is greater because the distribution of responses gave it a smaller average overall rank.

1,000 live births, whereas in California the fetal death rate is 8 per 1,000 births. The neonatal death rate reported by the group was 184 per 1,000 live births, in contrast to the California rate of 14 per 1,000. Infant deaths after 1 month of age and before the first birthday occurred at a rate of 18 per 1,000 births. Childhood deaths through age 18 were 36 per 1,000 births.

Knowledge of Family Planning Methods

To ascertain the knowledge of fertility control alternatives, questions were asked regarding specific family planning methods. Respondents were asked first whether they had ever heard of a method, and their responses were ranked for different family planning methods (Table 3). An overall average rank was determined for each ethnic group that did not depend on the different numbers of each ethnic group responding—an unweighted mean. The rank order of methods was highly correlated among ethnic groups of refugees and did not differ substantially by age, sex, year of entry, refugee screening clinic, or rural background.

In general, more people reported an awareness of the more effective methods (Table 4). Among the highly effective methods, oral contraceptives ("pill") and female sterilization (tubal ligation) ranked higher overall than an intrauterine device, male sterilization (vasectomy), or injectable medroxyprogesterone acetate (Depo-Provera) among those who said they were aware of the method. The Hmong were the least aware of contraceptive methods. More Lao Mien and Cambodians responded they had heard of oral contraceptives and female sterilization than did the Vietnamese ($P < .01$). More Cambodians and Vietnamese reported they knew of male sterilization than did the Lao Mien ($P < .01$). Fewer lowland Laotians had heard of the effective methods than had the Cambodian, Vietnamese, and Lao Mien refugees ($P < .001$), although more had heard of them than had the Hmong ($P < .01$).

Although medroxyprogesterone is not approved for use in the US by the Food and Drug Administration, 95% of Lao Mien, 93% of Cambodians, 65% of lowland Laotians, 43% of Vietnamese, and 24% of Hmong reported being aware of the method (see Table 4).

Among the other methods of contraception, only the condom appears to have substantial recognition (Table 4). Lowland Laotians responded significantly less often than Cambodians, Mien, and Vietnamese that they had heard of the condom (72%; $P < .001$), and Hmong responded even less often than the lowland Laotians (43%; $P < .0001$). The Mien were the only group in whom a majority (55%) knew of foam. Knowledge of the combined use of foam and condom was not ascertained in the study, although some of the interviewed refugees spontaneously responded that they were using or had used this combination.

Depth of Knowledge of Specific Family Planning Methods

Respondents who were aware of a method were asked if they knew how it was used (Table 5). While 90% knew of one or more of the more effective methods, only 49% indicated they knew how any of the methods was used, and most reported understanding only how oral contraceptives were used. Surgical methods, especially, were described in such general terms—often as an "operation," a word that was often supplied to clarify the question—that the description, though partially correct, was inadequate. Far fewer respondents who were aware of less effective methods were able to describe how they were used. Only 66% of those who said they knew how to use the rhythm method described the fertile period correctly.

Family Planning Practices

Of those who were not pregnant at the time of the study and who stated they did not want to get pregnant, 70% reported they were using a family planning method, and 64% of these were using one of the more effective methods. Thus, only 45% of those not wanting more children would be con-

TABLE 4.—*Extent of Knowledge of Specific Family Planning Methods*

Family Planning Methods	Aware of Method		Know How to Use Method		Described Use of Method Correctly or Partially Correctly	
	Number	Percent	Number	Percent	Number	Percent
More Effective Methods						
Oral contraceptives	298	88	141	54	135	53
Female sterilization	329	84	67	19	60	18
Intrauterine device	289	75	62	18	55	16
Male sterilization	285	73	48	13	46	13
Injectable	270	69	66	19	64	18
Subtotal	356*	90	184	49	173	46
Other Methods						
Condom	325	83	115	34	102	31
Fertility awareness (rhythm)	193	49	77	22	60	17
Foam	131	33	26	7	21	6
Abstinence	114	29	34	10	26	8
Withdrawal	136	35	64	18	50	15
Douche	110	28	35	10	33	9
Diaphragm	87	22	24	7	23	6
Suppository	78	20	19	5	16	4
Jelly	69	18	10	3	10	3
Subtotal	342	86	155	39	135	34
Total	363	91	225	60	203	54

*Fourteen people who answered "Aware" questions did not answer the "Know how to use" or "Describe use" questions.

sidered protected above a 97% effectiveness level by family planning methods.

Slightly more than half of the women in the study who were not already sterilized or infertile expressed a willingness to use family planning. Nearly a third (30%) said that they were not sure if they were interested, and 19% did not want to use a method of contraception. When those interested but not currently using a family planning method were asked when would be the best time to start, 46% responded after their next baby. Another 22%, when prompted, expressed that after all their babies were born would be a good time to start family planning.

Among those currently using contraception, 61% said that it was because they desired no additional children. The remaining 39% said that it was for spacing.

Past and Present Use of Specific Family Planning Methods

Of those using family planning methods, more people had used or were currently using the more effective methods (see Table 5). Most had had tubal ligations, while only 2% had relied on vasectomy. Nearly 90% of those who had had a tubal ligation also said that they preferred female sterilization to other methods. The use of the second most prevalent method, oral contraceptives, had been discontinued by 39% of users for health reasons. Condoms were being used by nearly as many as were oral contraceptives and at the time of the interview their use was the third most prevalent method. Rhythm, withdrawal, and abstinence had all been used at one time or another by 11% to 19% of those who had ever used family planning.

Specific Types of Barriers to Family Planning Information

Nearly 70% of the refugees said that they had had problems getting information on family planning (Table 6). The barriers to obtaining this information are those common to many low-income, non-English-speaking groups. Language was mentioned as a problem by 73%. Significantly greater proportions of Cambodians (92%) and lowland Laotians (66%) acknowledged language as a barrier than other ethnic groups ($P < .01$), and almost twice as many women as men reported language problems ($P < .0001$). The second most frequent barrier was not knowing enough about family planning to be able to ask questions (21%). Although men reported this less often, the proportions of men and women were not statistically different.

Other barriers to getting family planning information were related to physical access—cost, waiting time, transportation. A possible cultural barrier, the fear for women of being examined by a male physician, turned out to be a minimal problem, as did the fear of a physical examination.

Discussion and Conclusions

Empiric observations by health providers and preliminary surveys of the health status of these refugees indicate that structural barriers to health care and cultural factors both contributed to significant gaps in the use of available health services.[7,8] While many Southeast Asians have accepted western curative medicine and use modern along with traditional remedies, problems still arise frequently during interaction with western medical providers. Cultural preferences of Southeast Asian groups that may present problems in the medical setting include a dislike of medical intrusion into the body, such as an operation; an unwillingness to participate in procedures involving blood or blood loss; a preference for health care providers of the same sex as the client; and social conventions regarding eye contact, terms of address, and contact with certain parts of the body.[8,9]

The need for both family planning education and access to health services for refugees is shown by the notable gap between knowledge and practice revealed in our study of refugees attending county clinics. Only 70% of our respondents who were not pregnant and did not want to be pregnant were using a contraceptive method. Furthermore, while there was a generally high awareness of the more effective methods among those using contraceptives, only 45% were using one of the more effective methods. The findings indicate considerable variation, however, both within and among the major ethnic groups examined. While it is clear, therefore, that there is no typical Southeast Asian, recognition of certain measured differences between the major waves of refugee

TABLE 5.—*Past and Present Use of Family Planning Methods*

Family Planning Methods	Ever-Used Family Planning* Number	Ever-Used Family Planning* Percent	Currently Using Family Planning† Number	Currently Using Family Planning† Percent
More Effective Methods				
Oral contraceptives	108	31	29	9
Female sterilization	48	12	45	14
Intrauterine device	29	8	9	3
Male sterilization	7	2	3	1
Injectable	33	9	1	0
Subtotal	178‡	43	87*	28
Less Effective Methods				
Condom	86	23	23	7
Rhythm	74	19	22	7
Withdrawal	43	11	16	5
Abstinence	43	12	5	2
Foam	17	4	4	1
Douche	20	5	2	1
Jelly	2	1	0	..
Suppository	4	1	0	..
Diaphragm	2	1	0	..
Subtotal	151‡	39	48‡	15
Any Method	246‡	56	138‡	44

*Of 438 ever-married respondents.
†Of 312 nonpregnant, married respondents.
‡Totals and subtotals are less than the sum of all numbers because some people reported more than one family planning method.

TABLE 6.—*Barriers to Getting Birth Control Information*

Problem	Respondents* No.	Respondents* Percent
Language barrier	163	73
Did not know about family planning	48	21
Cost	36	16
Waiting time	23	10
Transportation	10	4
Male doctor	10	4
Fear of examination	6	3
Other	2	1
Unduplicated total	224	

*Respondents who indicated they had had a problem getting information on family planning (N=323) were prompted as to each of the possible types of problem listed above.

groups and among the five ethnicities studied in this largely second-wave group is important if the planning of education and services is to be appropriate to the specific needs of each subgroup. In general, while the contraceptive prevalence in our interview sample was 38%, comparisons of family size, fertility preferences, knowledge of reproductive physiology and contraceptive methods are closer to western norms among the Vietnamese, with the Hmong at the other end of the spectrum, and the Cambodians, lowland Laotian, and Mien generally in between.

It is clear from these reports and our own data that the fertility of refugees, particularly of second-wave refugees, in this country tends to reflect Asian more than American norms. Rumbaut and Weeks[3] have developed a conceptual model that takes into account the sociodemographic background, migration phenomena, and economic and cultural adaptation of these refugees in an excellent analysis of alternative patterns of fertility shifts that may be expected as adaptation to the US environment progresses. Our findings suggest that in applying this useful approach to policy determination and educational strategies to assist refugees in the assimilation process, ethnicity appears to emerge as the outstanding distinguishing factor within the refugee groups, while gender, rural or urban background, duration of residence in the United States, and refugee clinics attended are also significant variables.

In this study sample, 75% of the married women living with their husbands and not pregnant responded that they currently did not want any more children. Yet 15% did not appear to be aware that birth control methods can be used to prevent pregnancy, and of those who did profess awareness of family planning methods, further probing disclosed important gaps in the knowledge of how methods are actually used. While 90% of those responding that they knew of family planning were aware of at least one of the methods considered highly effective, only half reported that they knew how to use it, and only in the case of oral contraceptives were more than half able to describe its use correctly.

Among this group, many appeared to be unaware of available family planning services in their community or indicated that there were barriers to their use. The differences in the range of methods of which members of the various ethnicities are aware and the differences between the sexes within ethnic groups have implications for the content of educational approaches. This study underscores the need for specific information and education about both reproductive physiology and contraceptive methods. The fact that 78% of the sample responded that the decision to use family planning should be made jointly by husband and wife points to the need for counseling of couples and education in small groups, in addition to person-to-person communication. The ethnic and sex differences in knowledge, as well as the variation in individual sophistication, call for the provision of language- and culture-specific printed materials, including pictorial explanations where necessary. These are not generally available in busy clinics or private physicians' offices. Particular attention should be given to education in spacing methods, in view of our finding of a frequent conceptual association of family planning with completed family size. Despite the relatively young age distribution of our sample, with 55% of the women in the study younger than 30 years, 61% of those currently using a contraceptive method declared that they wanted no additional children, while 39% were using contraception for spacing.

In addition to the need for language- and culture-specific educational materials, the provision of services by specifically trained and selected personnel is needed. Moreover, as both reductions in funding levels and changes in policies affecting eligibility further limit access to health services for refugees, in-service training and continuing education of mainstream providers become increasingly important. Our study shows the important differences in contraceptive method preferences and in the attitudinal determinants of compliance with contraceptive regimens that distinguish the refugees from other family planning clients and that require sensitivity and understanding on the part of providers.

Serious attention in the public sector to constructive steps to reduce these barriers to access to effective family planning information for Southeast Asian refugees cannot be disregarded as a temporary need. The demand for family planning services will undoubtedly increase as the adaptation process progresses. The number of income-eligible refugees requiring subsidized services will remain high as the second wave of immigrants in particular requires a longer period of adjustment to achieve self-sufficiency. Finally, new arrivals of refugees from Southeast Asia continue, albeit at a lower rate than in years past, and will continue for the foreseeable future, as thousands of refugees still in camps have applied for permission to immigrate to the United States. The evidence of a high cost-benefit ratio for subsidized family planning services shows the economic wisdom of policies in support of such services to these deserving new members of American society.

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Public Health and Preventive Medicine

Joint California Department of Health Services-California Medical Association Campaign to Eliminate Congenital Rubella Syndrome

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This is one of a series of articles from western state public health departments.

The California Department of Health Services and the California Medical Association joined forces in 1986 for an ongoing effort to eliminate the remaining morbidity and mortality burden that the congenital rubella syndrome continues to impose in California.

The Current Rubella Problem

Great strides have been made in the past 19 years in the control of rubella through the widespread use of rubella vaccine. The incidence of both rubella and of the congenital rubella syndrome has declined more than 90% since the introduction of the vaccine in 1969.[1] Despite this success, rubella virus circulation continues in this country, and because of susceptibility among teenagers and young adults, pregnant women continue to be infected by the rubella virus, often with disastrous consequences for the fetus.

While fewer than a dozen cases of congenital rubella syndrome have been reported annually in the United States in the past few years, problems of underdiagnosis and underreporting lead to estimates that the actual incidence may be more than 100 cases a year.[2] The average lifetime medical and custodial care cost of a patient with congenital rubella syndrome is more than $220,000.[3] Moreover, for every infant reported as born with the syndrome, an estimated ten pregnancies are terminated by therapeutic abortion because of acute rubella infection.[4] Further, many more pregnant women suffer anxiety caused by exposure to rash illnesses that may or may not be rubella.

In California, a large rubella outbreak in 1979 was followed by a rise in reported cases from 9 in 1979 to 17 in 1980. Similarly, an outbreak in this state in 1982 was followed by a rise in reported cases from three that year to seven in 1983. Again, estimates are that for every reported case, there are ten unrecognized or unreported cases of children born with congenital rubella syndrome and ten therapeutic abortions done because of rubella infection in early pregnancy.

There were at least seven rubella outbreaks in California in the first half of 1986, six of them involving young adults primarily. Rubella outbreaks in medical facilities have been a particular problem in recent years. Rubella susceptibility is nearly 20% among young adults in California,[5] and hospitals and outpatient clinics frequently employ them in significant numbers, thereby facilitating the transmission of infection that has been introduced. More than ten reports of rubella outbreaks in medical facilities have been published, and many others have occurred, with some of these outbreaks leading to infection of pregnant women. Managing such outbreaks can be time-consuming and costly. In addition to isolating ill patients, the facility must follow up on exposed pregnant women—patients, staff, and household contacts of staff—to determine if they have been infected, keep exposed susceptible staff off work for the balance of the incubation period, keep susceptible pregnant staff off work for the duration of the outbreak, postpone clinics, and conduct emergency staff immunization campaigns. Pregnant women who are infected must be counseled regarding the risk to their fetuses and advised regarding the option of terminating their pregnancies.

The rigorous enforcement of school entry requirements for rubella immunization in all states is producing very high immunization levels among school-age children. Because most states enacted such requirements relatively recently, however, and because in many states this immunization requirement does not extend through the secondary school years for all pupils, it will be at least a decade before cohorts of well-protected young adults replace their less well-immunized predecessors, thereby achieving sufficient "herd immunity" in this age group. In states that receive large numbers of unimmunized adults from countries where rubella infection

(Dales L, Kizer KW, Elliott GV: Joint California Department of Health Services-California Medical Association campaign to eliminate congenital rubella syndrome. West J Med 1988 Mar; 148:355-357)

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is less common, the problem may continue even longer. In the interim, without programs to immunize young adults—especially women of childbearing age—preventable cases of the congenital rubella syndrome will continue to occur.

Efficacy and Safety of Rubella Vaccine

The live attenuated RA 27/3 strain of human diploid cell-cultured rubella vaccine currently used in this country produces seroconversion rates in excess of 99%.[6] So far, antibody persistence for more than 15 years has been documented, and lifelong protection is anticipated for the vast majority of vaccinees.[7,8] Rubella outbreak investigations have shown a vaccine efficacy in protecting against clinical illness ranging from 90% to 97%.[9]

While rubella immunization during pregnancy is to be avoided, accumulating data continue to show no observed fetal risk associated with inadvertent maternal immunization. In the United States, West Germany, and the United Kingdom, 335 infants born to susceptible women who had inadvertently received rubella vaccine shortly before or during early pregnancy have been examined; none had the syndrome.[10,11] While the final decision must rest with the individual patient and her physician, the United States Public Health Service Immunization Practices Advisory Committee states that the risk of vaccine-associated defects is negligible and that inadvertent rubella immunization ordinarily should not be a reason to consider interrupting a pregnancy.[12] Also, rubella vaccinees do not shed the virus, so that household contacts of pregnant women can be immunized without the risk of spreading the vaccine virus to the pregnant women.

As many as 40% of susceptible adult women who receive the rubella vaccine have reported transient joint complaints; among immune subjects receiving rubella vaccine, the incidence of arthralgia or arthritis is no greater than in placebo recipients.[13] In rare cases, susceptible women receiving rubella vaccine have experienced recurrent episodes of arthralgia or arthritis that continue for several years.[14] The information on these prolonged episodes of joint problems following adult immunization is mostly based on anecdotal observations, however. In addition, most of the small number of women with this problem are asymptomatic between these episodes, which gradually diminish in frequency and severity. No joint destruction has been documented. The United States Public Health Service Centers for Disease Control staff do not think these rare events indicate the need for any change in current immunization practices.[15]

Young-Adult Rubella Immunization Campaign

To reach the goal of eliminating the congenital rubella syndrome soon, increased emphasis will have to be placed on immunizing women of childbearing age. This recommendation applies specifically to the following groups:

- Women found on premarital serologic screening to be susceptible to rubella—premarital rubella immunity screening is required in California for women younger than age 50.
- Women found to be susceptible on prenatal screening. Vaccine should be given promptly at the conclusion of pregnancy, whether that conclusion is a live birth, stillbirth, or spontaneous or therapeutic abortion.
- Women patients in family planning clinics who are known or presumed to be susceptible.
- Women known or presumed to be susceptible on discharge from a hospital, unless a contraindication exists, or at the time of outpatient office visits.
- Men and women known or presumed to be susceptible at the time of employment in medical facilities—hospitals, outpatient clinics, physicians' offices—or at the time of employment in any setting where a large number of children or young adults aggregate: day-care facilities, schools, colleges, or large office buildings, for example.
- All students in colleges and universities.

Screening for Rubella Immunity and Administering Rubella Vaccine

Either single-antigen rubella vaccine, combined measles-rubella vaccine, or combined measles-mumps-rubella vaccine can be used. Because of the safety of reimmunizing with these vaccines,[12,16,17] the combined vaccines can be given to those already immune to one or more of the components.

Because of the absence of adverse effects from rubella immunization in persons who are already immune, serologic screening for susceptibility before immunization is generally not necessary.[12] Further, persons should be considered immune to rubella only if there is documented laboratory evidence of such immunity—the presence of serum rubella antibody, for example—or documented immunization with rubella vaccine on or after the first birthday. Because of the unreliability of a clinical diagnosis of rubella, a history of clinical rubella disease cannot be considered sufficient evidence of immunity.

Screening for rubella vaccine contraindications can be done by questioning a patient; physical examination and laboratory tests are not necessary. The following persons should not receive the vaccine:

- Anyone with an acute febrile illness. Persons with mild upper respiratory tract infections or in the convalescent phase of an acute illness can be immunized.
- Persons with a proven severe allergy to the antibiotic neomycin sulfate, manifested by collapse, shock, tongue or mouth and throat swelling, hypotension, respiratory distress, or urticaria. For those receiving rubella vaccine that is combined with measles or mumps vaccines or both, a severe allergy to eggs is also a contraindication.
- Persons who are significantly immunocompromised as a result of immune deficiency diseases, including the acquired immunodeficiency syndrome, leukemia, lymphoma, or generalized malignancy, or who are immunosuppressed as a result of high-dose systemic steroid therapy, cancer chemotherapy, or radiation therapy. However, steroid therapy of less than two weeks' duration and topical steroid therapy generally are not contraindications to immunization.
- Women who are pregnant or who are likely to become pregnant within the next three months are not to be given the rubella vaccine. An appropriate screening question is, "Is it possible that you are pregnant now or likely that you will become pregnant in the next three months?" Women who answer "no" can be immunized. It is not necessary to limit immunization to women with menses within the preceding two weeks or with a negative pregnancy test. As mentioned earlier, information gathered to date shows no evidence of fetal damage from immunization unintentionally given during pregnancy.

The California Department of Health Services and the

California Medical Association have developed English and Spanish informational leaflets on rubella immunization aimed at women of childbearing age. Physicians and clinics can order supplies of the leaflets, free of charge, by writing to the Immunization Unit, California Department of Health Services, 2151 Berkeley Way, Room 712, Berkeley, California 94704.

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Book Review

The Western Journal of Medicine *does not review all books sent by publishers, although information about new books received is printed elsewhere in the journal as space permits. Prices quoted are those given by the publishers.*

Atlas of Drug Reactions

Edited by R. Douglas Collins, MD, formerly Associate Clinical Professor of Medicine, University of Florida College of Medicine, Gainesville, and formerly Director, Internal Medicine Residency Program, Pensacola Foundation for Education and Research, Inc, Pensacola, Florida. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1986. 410 pages, $55.

Although Dr Collins dedicated his remarkable book, *Atlas of Drug Reactions,* to the family doctor, it is eminently practical for any medical specialist.

The book is "biologically appropriate." Reading it does not produce stress. It has a large, readable font (Times-Roman) with paragraph headings in large boldface type. The headings of all the principal drugs are listed on top of the pages under their generic and trade names. Adverse reactions are discussed and precautions recommended.

There is a lavish use of space, and yet none of it is wasted. The reader is provided with quick access to all the drugs currently being used. There is a colored plate, a sagittal section of a human, showing various organs such as the heart, lungs, liver, stomach, kidneys, bladder, and rectum. The plate also has a blood pressure gauge. Captions to the left of the diagram are connected with lines to the organs involved, and describe what particular problem is represented. For example, urinary retention has a line to the bladder, and mydriasis has a line to the iris. These colorful diagrams are extremely valuable in giving a preliminary idea of how the drug in question works. Also, the colored plate is repeated several dozen times. This repetition is quite acceptable and useful.

The book does not have the cramped dictionary style of most atlases. One experiences an immediate sense of relief on opening it, and the comfortable reading goes along with information that is thorough, scientific, and practical.

One of the most important things the book does is to provide information on drug interactions. This enables the physician to give patients advice about taking several drugs simultaneously and also compels the physician to ask the question: "What drugs are you taking, and when?" The headings also include contraindications, precautions, toxicity ratings, and treatment.

A toxicity rating—low, medium, or high—depends on the severity of the reactions. This is an extremely important addition to an atlas of this kind. There are headings on each drug under dermatologic, cardiovascular, gastrointestinal, hepatic, and other reactions.

There are two appendices, the first of which lists all the generic drugs and their therapeutic areas: disopyramide phosphate is listed as an antiarrhythmic agent; hydralazine hydrochloride, an antihypertensive; Oxytocin, a posterior pituitary hormone, and so forth.

The second appendix gives the generic names of all the drugs, along with their trade names, their classification, and any significant or serious drug reactions. For example, under the trade name of Anaprox, the generic name of naproxen sodium is given, the drug is classified as an antiinflammatory agent, and the significant or serious reaction is peptic ulcer. At the end of the book there is a detailed general index.

Dr Collins does not omit subjects that one might expect not to find in such an undertaking. He includes parasitic agents, topical otologic, nasal, and oral preparations, and dermatologic medications. There is also a complete list of biologicals such as antigens, antisera, extracts, toxoids, vaccines, and so forth.

Most of us have struggled with the tissue paper directions that come with drugs: the tiny print often requires the use of a magnifying glass, and the information succeeds in producing a kind of paranoia because the physician never really knows how safe the drug is and how to determine this. Dr Collins' book provides the physician with a secure kind of information that enables him to proceed with treatment without fear and with realistic information of what he might expect. Nobody can escape the statistical significance of a one in a half-million horrible happening, but one has to proceed with treatment, and the guidelines of Dr Collins' atlas are "state-of-the-art" in pharmacology.

One of the most important features of the book is the toxicity rating. Each drug is rated low, medium, or high in toxicity according to the frequency, severity, and reversibility of its adverse reactions. Quoting from Dr Collins' introduction, "Drugs such as sympathomimetics, antihistamines, and hypnotics are mostly rated low. On the other end of the spectrum are drugs such as aminoglycosides, which cause ototoxicity and nephrotoxicity, and phenylbutazone and chloramphenicol, which cause agranulocytosis. In between are a host of drugs with a medium to high rating, which require careful consideration before being prescribed. Some drugs have a moderate to high rating only when given parenterally."

This is more than a reference book. It provides an assortment of information that allows the physician to prescribe with caution and clearly states drug reactions and how to treat them. I found it a superb addition to my library, and since I began reading it, I have recognized a sense of security and efficiency in my approach to the problem of drug reactions. It has been a pleasure to be introduced to this remarkable atlas. It is extremely valuable, and I recommend it highly.

GERALD MASON FEIGEN, MD
San Francisco

Physicians on Trial—Self-Reported Reactions to Malpractice Trials

SARA C. CHARLES, MD
CHARLENE E. PYSKOTY, MA
AMY NELSON
Chicago

A MAJOR MEDICAL INSURER reported that the frequency of malpractice claims increased from 10.5 claims per 100 physicians in 1980 to 17.8 claims per 100 in 1986.[1] Not all claims involved litigation, and the number of cases that eventually went to trial was very small. As an example, the Illinois State Medical Inter-Insurance Exchange, a physician-owned insurer, since its inception in 1976 has tried to verdict less than 4% of its 8,965 closed claims, 96% of which involved a malpractice suit.[2]

In a literature review, no reports were given on the psychological reaction to being on trial for any cause. Our previous studies indicated that being sued for malpractice was stressful for most physicians and resulted in a number of physical, emotional, and behavioral responses. Few of these cases, however, had progressed to trial. We studied a group of physicians whose malpractice actions did result in trial in order to compare their responses with those of both sued and nonsued physicians previously studied.[3,4]

Physicians and Methods

A mail survey was sent to those physicians who were listed in the 1985 Cook County Jury Verdict Reporter summary and index of malpractice trials for northern Illinois.[5] Valid addresses were obtained for 107 of the 122 physicians who went to trial during that year. A total of 64 questionnaires were completed, for a response rate of 60%. The questionnaire was based on an instrument used previously, with questions added to request specific information about the trial.[3,4]

Statistical analysis included the use of the difference-of-proportions test to evaluate the significance of the differences between sued and nonsued physicians and between samples over time.[6(pp234-236)]

Results

Most of the responding physicians were men (N = 62, 97%), with a mean age of 50.6 years. The most frequently reported specialties were surgery (N = 25, 39%), internal medicine (N = 16, 25%), general practice or family practice (N = 11, 17%), and obstetrics and gynecology (N = 9, 14%). Most were board certified (N = 50, 78%), and 25% (N = 16) had been recertified. The most commonly mentioned types of practice were solo (44% [28]) and partnership or corporation (39% [25]). Locations of practices were suburban (52% [33]), urban (38% [24]), and rural (8% [5]). Age, sex, specialty, and certification percentages were comparable to our previous studies.[3,4]

The percentage of physicians (72% [46]) who won favorable verdicts is comparable to that noted in other reports.[7(p22),8(p51)] Almost 45% (28) had known the plaintiff-patient one month or less, while about 17% (11) had known the patient for more than five years. In all, 47 (73%) physicians, compared with only 34 (53%) in our first study, reported additional malpractice suits filed against them. Of these, 11 reported five or more suits.

Symptomatic Reactions

Most (97%) of these physicians acknowledged some physical or emotional reactions, or both, in response to being sued for malpractice. Ten (16%) said that the trial was the single most stressful stage of litigation. Most (52% [33]) indicated that the entire period or a combination of stages was most stressful (Table 1). Feelings of inner tension (86% [55]), depressed mood (80% [51]), frustration (78% [50]), and anger (70% [45]) were commonly reported (Table 2).

About 58% (37) of all respondents acknowledged either one or both of the symptom clusters that we described in earlier studies.[3,4] Of these, 53% (34) reported the anger cluster of symptoms (with or without the depressive cluster), which is characterized by feelings of anger accompanied by at least four of the following symptoms: depressed mood, inner tension, frustration, irritability, insomnia, fatigue, headache, or gastrointestinal symptoms. This percentage included 67% who lost at trial and 48% of those who won. Only 5% (3), including both those who won and those who lost, reported the depression cluster alone (exclusive of the anger cluster), which is characterized by a depressed mood accompanied by at least four of the symptoms from the criteria list for affective disorder in the *Diagnostic and Statistical Manual of Mental Disorders,* revised third edition.[9] The differences in self-reported symptoms and symptom clusters between those who won and those who lost were not significant.

Although the majority (88% [56]) of the total sample believed that a plaintiff's case was not justified, the physicians who lost were significantly more likely than those who won to feel that the plaintiff's case was indeed justified ($\chi^2 = 5.89$, degrees of freedom 1, $P = .015$). Those who lost also tended to report more feelings of guilt ($\chi^2 = 2.98$, df 1, $P = .086$) and were significantly more likely to report a lack of adequate social support ($\chi^2 = 5.45$, df 1, $P = .019$).

There was notably less physical illness but more insomnia reported by physicians in this study compared with the sued groups previously studied. On almost every variable there were significant differences between the groups of sued physicians and the one group who had not been sued (Table 2).

Changes in Practice Behavior

Physicians in this study, compared with sued physicians in previous studies, reported similar changes in their daily medical practice (Table 2). Furthermore, the number of practice changes that were initiated was significantly and positively correlated with the number of symptoms reported ($r = .4952$,

(Charles SC, Pyskoty CE, Nelson A: Physicians on trial—Self-reported reactions to malpractice trials. West J Med 1988 Mar; 358-360)

From the Department of Psychiatry, University of Illinois School of Medicine (Dr Charles and Ms Pyskoty), and the Department of Psychology, Loyola University (Ms Nelson), Chicago.

This research was sponsored by a grant from the Doctors' Company, Santa Monica, California.

Reprint requests to Sara C. Charles, MD, Department of Psychiatry, University of Illinois at Chicago, 912 S Wood St, Chicago, IL 60612.

$P < .001$). Nearly 90% (57) of those studied indicated that the current climate of litigation has eroded the quality of the physician-patient relationship. More of them were likely to question their competence as a result of litigation than the sued physicians in the first study, but compared with nonsued physicians, they were less likely to do so. Almost two thirds reported a decreased satisfaction with their careers.

Discussion

The results of this study indicate that, in terms of symptomatic and behavioral responses to malpractice litigation, it does not matter whether a physician goes to trial or even whether he or she is vindicated by a favorable trial outcome. In addition, as shown by comparing these results with our previous studies, those who have been sued, regardless of the phase of litigation or the outcome of the suit, generally report significantly more adverse symptoms and changes in behavior than nonsued physicians.

Compared with our earlier studies, a smaller percentage of physicians reported that they have stopped seeing certain types of patients, and significantly fewer reported that they stopped doing certain high-risk procedures and had changed their record-keeping as a result of litigation. This may simply represent a function of time. The process of litigation is lengthy—the average length of time in this study from complaint to trial was 37.5 months. These physicians may have initiated changes in practice early in the process that they may no longer perceive as changes. On the other hand, this decrease may represent a certain attitude, not clearly measured, that is unique to physicians who experienced the entire litigation process, even though most won their cases. They may feel, for example, that engaging in such behavior has no relationship to the risk of being sued. Although fewer than in previous studies reported making changes in their practices, the total number of physicians who report defensive practice behavior remains quite high.

Among current study subjects there was a dramatic increase in the anger cluster of symptoms, whereas the depression cluster was significantly lower than in our previous studies. These changes may be due to a number of factors. In the 1982 study, for example, 64% of respondents were sole defendants; in the current study, only 28% were. Being accused as one of a group or in conjunction with a hospital may dilute the feelings of isolation so commonly reported in our earlier studies. This may generate more anger but less depression.

There also have been changes in the attitude of physicians regarding the commonly accepted notion that a malpractice suit represents a judgment on one's competence. As shown in Table 2, the nonsued in one of our earlier studies were significantly more likely than all three groups of sued physicians to feel that, given the threat of being sued for malpractice, litigation is both an affront to and a reflection of one's professional competence. This attitude, similarly held by the lay public, implies that a malpractice suit is directly related to negligence or lack of competence and is, therefore, the physician's "fault." On the other hand, once a physician is sued, these feelings about the relationship between competence and malpractice suits may change, often because in the incident in question, the physician felt that he or she had exercised good judgment and behaved in a competent manner. This change in attitude may set the stage for more feelings of anger and frustration that are externally directed toward a system in which highly competent physicians are the ordinary subjects of malpractice suits. At the same time, fewer physicians would experience the internally directed feelings of depression,

TABLE 1.—*Most Stressful Stage of Litigation Process*

Stressor	*Physician Response, N=64 No. (%)*
Notification	13 (20)
Period of discovery	2 (3)
Trial	10 (16)
Entire period	21 (33)
Combination of stages	13 (20)
No particular stage mentioned	5 (8)

TABLE 2.—*Symptomatic and Behavioral Responses to Malpractice Litigation—Comparison of Three Studies*

	*1982**	*1983†*		*1986‡*
	N=154, %	*Sued N=194, %*	*Nonsued N=152, %*	*N=64, %*
Did unnecessary tests	62	68	60	67§
Changed record keeping	69§	75	79	56§‖
Stopped seeing certain patients	48§	49§	30	41
Stopped doing high-risk procedures	28	43§	33	14§‖
Questioned own competence	15§	39§	59	31§‖
Talked with peers	10§	..	..	70‖
Inner tension	74§	83§	57	86§
Depressed mood	72§	79§	51	80§
Frustration	70§	77§	48	78§
Anger	88§	86§	46	70§‖
Insomnia	47§	56§	43	56§‖
Onset of physical illness	8	5	6	2‖
Exacerbation of physical illness	7	10	9	2§‖
Depression cluster	39§	35§	27	27‖
Anger cluster	20	31§	14	53§‖

*From Charles et al.[3]
†From Charles et al.[4]
‡This study.
§$z > 1.65$, $P < .05$; sued physicians differ significantly from nonsued.
‖$z > 1.65$; $P < .05$; data from this study differ significantly from those of Charles and co-workers.[3]

guilt, and shame that commonly accompany the accusation of being a "bad doctor."

Social support may also play a role in the expression of symptoms. In our 1982 study, only 10% of those responding said that they talked about the emotional impact of litigation with one of their peers, compared with more than 70% of the current study subjects. The forming of medical and specialty society support groups that provide a resource of understanding for those involved in litigation reflects this development.[10] Sharing the emotional impact of this event with a colleague allows for a greater expression of anger and may at the same time diminish the potential for turning the anger inward, a classic explanation for the development of symptoms of depression.[11(p400)] Although this study showed no significant differences in symptoms between physicians who won and those who lost their trials, the latter clearly felt they had less social support. A legal judgment of malpractice, irrespective of one's real level of competence, may set in motion self-generated behaviors that disrupt these physicians' perception of their own social roles and status. This may also alter their feelings of community with other medical professionals. This finding may give added direction to support groups by identifying a particularly vulnerable group—those who lost at trial—who may profit from active interventions even though they evince no more symptoms than their vindicated counterparts.

Some researchers have suggested that a feeling of well-being is an important variable in determining the quality of care delivered by a physician.[12] As noted earlier, an increasing number of practicing physicians have become subjects of litigation. If, as the findings of this study suggest, the major impact of the litigation experience—in terms of physical, emotional, and behavioral changes—is a function of the allegation rather than the outcome of the suit, and because the number of practice changes initiated was significantly and positively correlated with the number of symptoms reported, then this increase in allegations may have important implications for the quality of medical care. We plan further studies to quantify the specific effects that litigation has on a physician's feeling of well-being and its subsequent effect on patient care.

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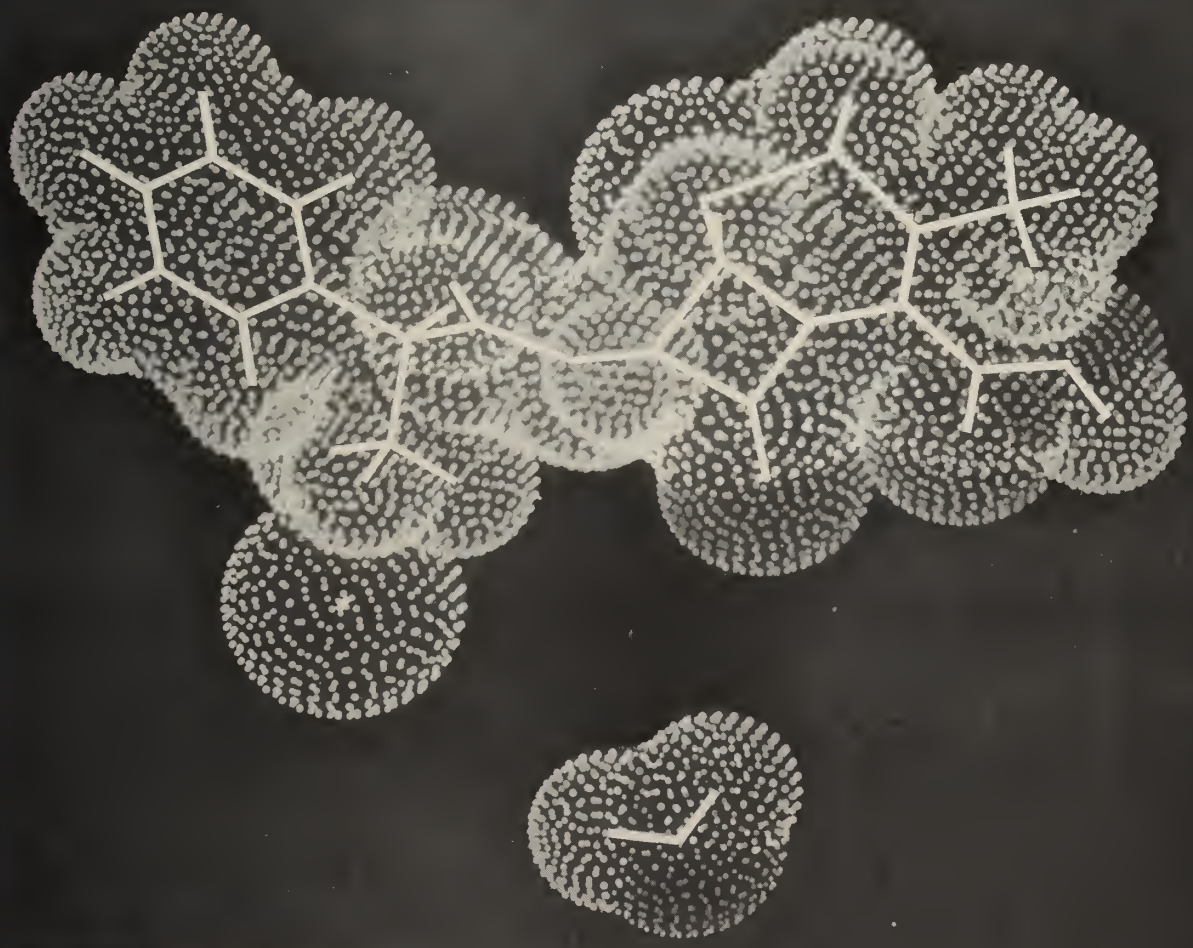

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CONTINUING MEDICAL EDUCATION

(Continued from Page 294)

May 12-14—**Modern Concepts in Trauma Care Symposium.** Orange County Trauma Society at Disneyland Hotel, Anaheim. Thurs-Fri. 18 hrs. Contact: Orange County Trauma Society, (800) 368-0911.

June 6-10—**Topics in Emergency Medicine.** UCSF at Holiday Inn, Union Square, San Francisco. Mon-Fri. 32 hrs. $420. Contact: UCSF.

August 29-September 2—**Topics in Emergency Medicine.** UCSF at Holiday Inn Union Square, San Francisco. Mon-Fri. 31 hrs. $420. Contact: UCSF.

INTERNAL MEDICINE

March 16-19—**Frontiers in Clinical Rheumatology.** UCD at Clarion Inn, Napa. Wed-Sat. Contact: UCD.

March 17-18—**Diseases of the Urinary Tract.** Stanford University Medical Center at Hyatt Rickeys Hotel, Palo Alto. Thurs-Fri. 15 hrs. $300. Contact: Stanford.

March 18-20—**6th Carl M. Person Memorial Symposium: Frontiers of Rhematology.** Annenberg Center for Health Sciences at Palm Springs. Fri-Sun. 15.5 hrs. Contact: Annenberg Center, 39000 Bob Hope Dr, Rancho Mirage, 92270-3298. (800) 321-3690.

April 9-16—**16th Annual Diagnostic and Therapeutic Skills in Internal Medicine.** USC at Mauna Kea Beach Hotel, Hawaii. One week. 29 hrs. $545. Contact: USC.

April 16-23—**Internal Medicine.** Stanford University Medical Center at The Westin Mauna Kea, Hawaii. Sun-Fri. 25 hrs. $495. Contact: Stanford.

May 23-27—**Advances in Internal Medicine.** UCSF at Sheraton-Palace Hotel, San Francisco. Mon-Fri. 32 hrs. $440. Contact: UCSF.

May 27-29—**California Society of Internal Medicine Annual Meeting** at Nikko Hotel, San Francisco. Fri-Sun. Contact: Kathy Matikonis, California Society of Internal Medicine, PO Box 880606, San Francisco, 94188-0606. (415) 882-5198.

June 6-10—**Advances in Internal Medicine.** UCSF at Cole Hall. 32 hrs. $440. Contact: UCSF.

June 15-17—**Gastroenterology: Advances in Diagnosis and Management.** UCSF at The Mark Hopkins Hotel, San Francisco. Wed-Fri. 17 hrs. $375. Contact: UCSF.

September 22-24—**International Symposium on Medical Virology.** UCI at Ramada Renaissance Hotel, San Francisco. Thurs-Sat. Contact: Dr Luis M. de la Maza, Department of Pathology, Rt 84, UCI Medical Center, 101 City Drive S., Orange, 92668. (714) 634-6868.

OB/GYN

March 16-19—**5th Annual Horizon in Reproductive Health Medical Conference.** UCSD at Hotel del Coronado, Coronado. Wed-Sat. Contact: Mary Fessel, 2100 5th Ave., San Diego, 92101. (619) 231-6760.

March 25-26—**GYN/Urology.** UCI at Hilton Riviera, Palm Springs. Fri-Sat. Contact: UCI.

April 21-23—**10th Annual Orange County OB/GYN Congress.** Orange County Obstetrical and Gynecological Society at Westin Hotel, South Coast Plaza, Costa Mesa. Thur-Sat. 15 hrs. $300. Contact: Paula Rogers, PO Box 1297, Orange 92668. (714) 978-1260.

June 30-July 3—**6th Annual Controversies in Obstetrics & Gynecology.** Center for Health Education at Mauna Kea Beach Hotel, Hawaii. Thur-Sun. Contact: The Center for Health Education, 2081 Atlantic Ave., PO Box 1428, Long Beach, 90801-1428. (213) 595-3811.

August 19-21—**1988—Office Gynecology for the Primary Care Physician.** Continuing Medical Education Associates and San Diego State University at Hyatt Islandia, San Diego. Fri-Sun. 18 hrs. $295. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

OPHTHALMOLOGY

March 18—**Visions in Ophthalmology '88.** Scripps Memorial Hospital at La Jolla Marriott, San Diego. Fri. 6 hrs. $75. Contact: Nomi Feldman, Conference Coordinator, 3770 Tansy St, San Diego 92121. (619) 453-6222.

(Continued on Page 363)

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CONTINUING MEDICAL EDUCATION

(Continued from Page 362)

PEDIATRICS

March 18-19—**Hematology: Neonatal, Pediatric & AIDS Related Issues.** Children's Hospital Oakland at Berkeley Marina Marriott Hotel, Fri-Sat. 11 hrs. Contact: Kim Leadon, CME Dept. Children's Hospital, 747 52nd Street, Oakland 94609. (415) 428-3021.

April 8-9—**UCD Annual Pediatrics Program.** UCD at Red Lion Motor Inn, Sacramento. Fri-Sat. Contact: UCD.

April 29-30—**21st Annual Advances and Controversies in Clinical Pediatrics.** UCSF at Mark Hopkins Hotel, San Francisco. Fri-Sat. 16.5 hrs. Contact: UCSF.

August 22-24—**Pediatrics Update: 1988.** San Diego State University at Hyatt Islandia, San Diego. Mon-Wed. 18 hrs. $295. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

October 22-29—**13th Annual Pediatrics for the Practitioner: A Pediatric Symposium.** Center for Health Education at Mauna Kea Beach Hotel, Hawaii. One week. Contact: The Center for Health Education, PO Box 1428, Long Beach 90801-1428.

PSYCHIATRY

March 27-31—**Adapting to Social Change, Therapy, Technology and Services.** American Orthopsychiatric Association at Hilton Square, San Francisco. Sun-Thurs. Contact: ORTHO, 19 W 44th St, #1616, New York, NY 10036. (212) 354-5770.

April 15-16—**3rd Annual Work and Mental Health Symposium.** UCSF at Holiday Inn Union Square, San Francisco. Fri-Sat. 12 hrs. $200. Contact: UCSF.

April 23-24—**The Cutting Edge 1988: Innovations in Psychotherapy: Helping Individuals and Couples to Change.** UCSD at Hotel Del Coronado, San Diego. Sat-Sun. 13 hrs. $275. Contact: UCSD.

May 23-24—**Child Abuse.** UCD at Holiday Inn Holidome, Sacramento. Mon-Tue. Contact: UCD.

RADIOLOGY

April 10-15—**8th Annual San Diego Resident's Radiology Review Course.** UCSD at Town & Country Hotel, San Diego. Sun-Fri. Contact: Mary J. Ryals, PO Box 920113, Norcross, GA 30092-0113. (404) 641-9773.

April 29-May 1—**13th Annual Spring Diagnostic Ultrasound Conference.** Los Angeles Radiological Society at Century Plaza Hotel, Los Angeles. Fri-Sun. 20 hrs. $325. Contact: Christopher M. Rose, MD, c/o Los Angeles Radiological Society—SDUC, PO Box 91215, Los Angeles 90009-1215. (213) 642-0921.

May 3-7—**8th Annual Post Conference Seminar.** Los Angeles Radiology Society at Kahala Hilton Hotel, Honolulu. Tues-Sat. 19 hrs. $395. Contact: Christopher Rose, MD, c/o Los Angeles Radiological Society—SDUC, PO Box 91215, Los Angeles 90009-1215. (213) 642-0921.

July 28-31—**Second Annual Symposium on Magnetic Resonance Imaging.** Hoag Memorial Hospital at Ritz-Carleton Hotel, Laguna Niguel. Thurs-Sun. $395. Contact: Mary J. Ryals and Associates, PO Box 920113, Norcross, GA 30092-0113. (404) 641-9773.

August 1-5—**Modern Radiology Practice.** UCSD at Fess Parker Red Lion Resort, Santa Barbara. Mon-Fri. 30 hrs. $425. Contact: Mary J. Ryals and Associates, PO Box 920113, Norcross, GA 30092-0113. (404) 641-9773.

August 25-28—**Fourth Annual Physics and Biology of Radiology.** UCSD at La Jolla Village Inn. Thurs-Sat. 25 hrs. $395. Contact: Mary J. Ryals and Associates, PO Box 920113, Norcross, GA 30092-0113. (404) 641-9773.

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September 9-11—**Fourth Annual Sonography Update and Review Course.** UCSD at Hanalei Hotel, San Diego. Fri-Sun. 17 hrs. $375. Contact: Mary J. Ryals and Associates, PO Box 920113, Norcross, GA 30092-0113. (404) 641-9773.

SURGERY

March 17-20—**The International Symposium on Hair Replacement Surgery.** American Academy of Facial Plastic and Reconstructive Surgery at Four Seasons Hotel, Los Angeles. Thurs-Sun. 30 hrs. Contact: AAFPRS Foundation, 1101 Vermont Ave. NW, Suite 404, Washington, DC, 20005.

April 14-16—**Postgraduate Course in General Surgery.** UCSF. Thur-Sat. Contact: UCSF.

April 15-17—**The 5th Annual San Diego Meeting on Arthroscopic Surgery of the Shoulder.** Tri-City Orthopaedic & Sports Physical Therapy Medical Group, Inc. at La Jolla Marriott Hotel, La Jolla. Fri-Sun. Contact: James C. Esch, MD, 3905 Waring Rd, Oceanside 92056. (619) 724-9000.

April 16-23—**Management of the Surgical Patient.** Stanford University Medical Center at The Westin Mauna Kea, Hawaii. Sun-Fri. 25 hrs. $495. Contact: Stanford.

April 29—**Ultrasonic Liver Surgery: A Hands-on Workshop.** UCD at Hyatt Regency, Sacramento. Fri. 8 hrs. $250. Contact: UCD.

June 20-24—**First International Symposium on Orbital Plastic Surgery.** Plastic Surgery Education Foundation at San Francisco. Mon-Fri. Contact: PSEF, 233 N. Michigan Ave, Suite 1900, Chicago, Illinois 60601.

August 18-21—**Discussions of Current Hand Care Concepts.** Plastic Surgery Education Foundation at San Diego. Thurs-Sun. Contact: PSEF, 233 N. Michigan Ave, Suite 1900, Chicago, Illinois 60601.

September 17—**Summary of Clinical Use of Argon, YAG and CO2 Lasers for Cutaneous Lesions.** Palo Alto Medical Foundation at Palo Alto Medical Clinic. Sat. 6 hrs. Contact: Palo Alto Medical Clinic, 300 Homer Ave, Palo Alto 94301. (415) 321-4121.

OF INTEREST TO ALL PHYSICIANS

March 16-18—**The Management of the AIDS Patient in Hospital and Outpatient Settings: An Action Plan for the Future.** The Healthcare Forum at The Nikko Hotel, San Francisco. Wed-Fri. $450. Contact: Howard Horwitz, The Healthcare Forum, (415) 421-8810.

March 16-19—**5th Annual Horizon in Reproductive Health Medical Conference.** UCSD at Hotel Del Coronado, Coronado. Wed-Sat. Contact: Mary Fessel, 2100 5th Ave., San Diego, 90101. (619) 231-6760.

March 18-19—**Hematology: Neonatal, Pediatric and AIDS Related Issues.** Children's Hospital, Oakland at Berkeley Marina Marriott Hotel. Fri-Sat. 11 hrs. Contact: Kim Leadon, CME Department, Children's Hospital, 747 52nd St, Oakland 94609. (415) 428-3021.

March 19—**3rd Annual Symposium on Women's Health.** Sutter Health at Board of Realtors Building, Sacramento. Sat. 6 hrs. $45. Contact: Sutter Health, CME Department, 2020 I St, Suite D, Sacramento 95414. (916) 446-7681.

March 19—**Inpatient Vs. Outpatient Treatment: How to Decide.** California Society for the Treatment of Alcoholism & Other Drug Dependencies at Ramada Renaissance Hotel, San Francisco. Sat. Contact: Corinne Parker, 3803 Broadway, Suite 2, Oakland, 94611. (415) 428-9091.

March 19-21—**Transfusion—Associated Infections and Immune Response.** UCSF at Fairmont Hotel, San Francisco. Sat-Mon. Contact: UCSF.

March 25—**Infectious Diseases for Pulmonary and Critical Care Specialists.** UCSF and Samuel Merritt Hospital at San Francisco. Fri. 7 hrs. $170. Contact: UCSF.

March 25-26—**Toxicology and Infectious Disease.** UCLA at San Diego Hilton Beach & Tennis Resort. Fri-Sat. 9 hrs. $146.25. Contact: UCLA.

March 26—**7th Annual Nora Eccles Harrison Symposium.** UCLA at Los Angeles. Sat. 7 hrs. $45. Contact: UCLA.

March 26-April 2—**Orthopedic Emergencies.** Scripps Memorial Hospital, Encinitas and American Institute of Postgraduate Education at Waiohai and Poipu Beach Hotels, Kauai. One week. 21 hrs. $395. Contact: Edith S. Bookstein/AIPE, PO Box 2586, La Jolla 92038. (619) 454-3212.

March 26-April 2—**Behavioral Medicine for the Family Physician.** University of Arizona at Kona, Hawaii. One week. 24 hrs. Contact: Kathy Rairigh, Epic Expeditions, P.O. Box 209, Sun Valley, Idaho 83353. (208) 788-4995.

April 10-12—**Symposium on Advanced Wound Care.** The Health Management Publications, Inc. at Hyatt Regency Hotel, Long Beach. Sun-Tues. 13 hrs. $250. Contact: Health Management Publications, Inc., 649 S. Henderson Rd, King of Prussia, PA 19406. (215) 337-4466.

April 10-15—**Advanced Methods in Pharmacokinetics and Pharmacodynamics.** UCSF. Sun-Fri. Contact: UCSF.

April 13-15—**9th Annual Advances in Infectious Diseases: Current Therapy.** UCSF at Sheraton-Palace Hotel, San Francisco. Wed-Fri. 16 hrs. $365. Contact: UCSF.

April 13-17—**Annual Scientific Program and Postgraduate Courses.** Pacific Coast Fertility Society at Desert Princess Resort, Palm Springs. Wed-Sun. 22 hrs. Contact: Pacific Coast Fertility Society, 5820 Wilshire Blvd, #500, Los Angeles 90036. (213) 937-5514.

April 15-17—**Office Orthopedics for the Primary Care Physicians.** CMEA & Sharp Memorial Hospital at San Diego Princess Hotel. Fri-Sun. 20 hrs. $395. Contact: Jacqueline Shiller, P.O. Box 84296, San Diego, 92138. (619) 223-2997.

April 16-23—**Current Concepts in Allergy and Clinical Immunology.** University of Washington at Maui, Hawaii. One week. Contact: U/W School of Medicine, Div of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

April 22-23—**Comprehensive Care of the AIDS Patient: A Workshop.** UCSF at San Francisco. Fri-Sat. Contact: UCSF.

April 23—**Current Concepts in Liver Diseases.** Scripps Clinic and Research Foundation at Amphitheater, Scripps Clinic, La Jolla. Thur. 6 hrs. $125. Contact: Bonny Mower, 10666 N. Torrey Pines Road, La Jolla, 92037. (619) 457-8556.

May 6-8—**Diagnosis and Management of Respiratory Diseases.** Medical Education Resources at Ceasars Palace, Las Vegas, Nevada. Fri-Sun. 11-13 hrs. $225-$295. Contact: MER, 5080 S. Rapp St., Suite 202, Littleton, CO 80120. (800) 421-3756.

May 12-15—**Decentralized Care of People With AIDS: An Educational Seminar for Developmental Approach.** Sonoma County Academic Foundation for Excellence at Flamingo Hotel, Santa Rosa. Thurs-Sun. $275. Contact: Mary Ellen Buechter, SCAFE, 3325 Chanate Rd, Santa Rosa, 95404. (707) 527-4121.

May 15-20—**Primary Care Medicine: Update '88.** UCSF at the Waiohai Hotel, Hawaii. Sun-Fri. 20 hrs. $425. Contact: UCSF.

May 26-27—**Current Concepts of Anatomic Pathology.** UCSF. Thur-Fri. Contact: UCSF.

June 11-12—**Procedure Skills for Primary Care Physicians.** Current Concept Seminars at Ibus Hotel, Milbrae. Sat-Sun. Contact: Donald Berman, MD, Current Concept Seminars, 3301 Johnson St, Hollywood, Florida 33021. (305) 966-1009.

June 13-17—**Family Practice Refresher Course.** UCI at Sheraton Newport, Newport Beach. Mon-Fri. 44.5 hrs. $575. Contact: UCI.

June 13-18—**UCI Family Practice Refresher Course.** UCI and Memorial Medical Center at Sheraton Newport Hotel, Newport Beach. Mon-Sat. Contact: Memorial Medical Center, PO Box 1428, Long Beach 90801-1428. (213) 595-3811.

June 18-19—**Skills Workshop: Flexible Sigmoidoscopy and Colposcopy.** UCI at Sheraton Newport, Newport Beach. Sat-Sun. 16 hrs. $140-ea., $250-both. Contact: UCI.

June 25-26—**10th Annual Poison Control Center Symposium on Toxicology and Poisoning.** UCSF and Continuing Medical Education in Pharmacy at San Francisco. Sat-Sun. 14 hrs. $235. Contact: Continuing Education S/P, UCSF, Box 0446, San Francisco 94143. (415) 476-4194.

July 14-17—**Decentralized Care of People With AIDS: An Educational Seminar for Developmental Approach.** Sonoma County Academic Foundation for Excellence at Flamingo Hotel, Santa Rosa. Thurs-Sun. $275. Contact: Mary Ellen Buechter, SCAFE, 3325 Chanate Rd, Santa Rosa, 95404. (707) 527-4121.

(Continued on Page 372)

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NEUROLOGIST. Visalia Medical Clinic, Inc, a 37 physician multispecialty group, is searching for a Neurologist to enter an active practice. Located in the San Joaquin Valley in California and serving a market area of approximately 350,000. Excellent hospital services and facilities. BC/BE. Compensation is incentive oriented with rapid advancement to full partnership. Excellent fringe benefits. Please respond to John G. Heinsohn, Administrator, 5400 W. Hillsdale, Visalia, CA 93291; (209) 733-5222.

DERMATOLOGIST. Visalia Medical Clinic has an opening for a BC/BE Dermatologist now staffed by one physician who has been with the Clinic for 15 years. Located in the San Joaquin Valley in central California and population approximately 350,000. Progressive city of 62,000, near national parks and the ocean. Compensation is incentive oriented with advancement to full partnership after one year. Excellent fringe benefits. If interested, CV to John G. Heinsohn, Administrator, 5400 W. Hillsdale, Visalia, CA 93291; (209) 733-5222.

OB/GYN. Multispecialty group in northwest Washington desires second Obstetrician. Excellent practice opportunity, full range of benefits, early partnership status, all practice costs paid. For more information contact Shane Spray, Administrator, 1400 E. Kincaid, Mount Vernon, WA 98273; (206) 428-2524.

INTERNIST NEEDED FULL-TIME. Primary Care position for Board certified Internist is now available with a growing San Francisco Health Plan. The position includes both inpatient and outpatient responsibilities. Send CV to Medical Director, French Health Plan, 4131 Geary Blvd, San Francisco, CA 94118.

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CALIFORNIA. Emergency Medicine Faculty Positions. Immediate opportunities available for career-oriented Emergency Physicians who possess excellent clinical and teaching skills to join the faculty of Emergency Medicine department. BC in Family Practice, Internal Medicine, Surgery, and/or BE in Emergency Medicine. Our facility, located in southern California, averages 38,000 Emergency department visits per year, is a level II trauma center, regional burn center and neonatology intensive care center. These positions require a teaching commitment in a university-affiliated Family Practice training program. We offer a competitive remuneration package to include salary, malpractice insurance, time off, and flexible scheduling. Send CV to Empire Medical Group, PO Box 3571, San Bernardino, CA 92413.

NEUROSURGERY. Visalia Medical Clinic has an opening for a BC/BE Neurological Surgeon to enter an immediate and active practice. Located in the San Joaquin Valley of California, serving a market area of approximately 350,000 citizens. Two Neurosurgeons presently serving this area. Excellent hospital services and facilities. Must be BC/BE. Compensation is incentive oriented with advancement to full partnership after one year. Excellent fringe benefits. John G. Heinsohn, Administrator, 5400 W. Hillsdale, Visalia, CA 93291; (209) 733-5222.

FAMILY PRACTITIONER. Visalia Medical Clinic has an opening for a BC/BE Family Practitioner to join a four physician department. Located in the San Joaquin Valley of California, serving a market area of approximately 350,000 citizens, the Visalia Medical Clinic is a 40 physician multispecialty clinic. Excellent hospital services and facilities. Compensation is incentive oriented with advancement to full partnership after one year. Excellent fringe benefits. John G. Heinsohn, Administrator, 5400 W. Hillsdale, Visalia, CA 93291; (209) 733-5222.

INTERNIST. To join two Primary Care Internists in private practice in beautiful far-northern California one hour below major center. Midway between Portland and San Francisco, we have a rural setting with sophisticated practice and excellent hospital facilities. Subspecialty interest desirable within primary care framework. Salary and benefits with partnership an early goal. CV and your interests to R. H. Alley, Jr, MD, 105 Oberlin Rd, Yreka, CA 96097.

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INTERNIST BC/BE to join Internist/Cardiologist in central California near Fresno. Reply to Number 85, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

PEDIATRICIAN. Visalia Medical Clinic has an opening for a BC/BE Pediatrician to join a five physician department. Located in the San Joaquin Valley of California, serving a market area of approximately 350,000 citizens, the Visalia Medical Clinic is a 40 physician multispecialty clinic. Excellent hospital services and facilities. Compensation is incentive oriented with advancement to full partnership after one year. Excellent fringe benefits. Contact Dr. James Simpson, 5400 W. Hillsdale, Visalia, CA 93291; (209) 733-5222.

NEAR STANFORD. Six Internists, all subspecialty trained and members of clinical faculty at Stanford, interested in an Associate with subspecialty interest and training. Should be well grounded in Internal Medicine. Send CV to Dr Bigler, El Camino Internal Medical Group, 125 South Dr, Mountain View, CA 94040.

BC/BE INTERNIST to associate with General Surgeon, OB/GYN, Pediatrician, Internist, and three FPs in well-established rural practice. Send CV to R. F. LeBlond, MD, Park Clinic, Box 1139, Livingston, MT 59047.

GENERAL INTERNIST needed for large hospital-based multispecialty clinic. University associated residency program. Attractive salary and complete benefit package. Pleasant setting. BC/BE. California license required. Contact Dennis L. Ostrem, MD, Chief Internal Medicine, The Permanente Medical Group, Inc, PO Box 254999, Sacramento, CA 95865-4999 or call (916) 973-5781. An Equal Opportunity Employer.

ARIZONA INTERNAL MEDICINE PHYSICIAN to associate with two man Internal Medicine group in Tucson. New office building with lab and x-ray. Well established practice. Sub-specialties welcome, BC/BE. Send CV to A. Oaks, 5265 E. Knight Dr, Tucson, AZ 85712.

EMERGENCY GROUP seeking career oriented ACLS, ATLS physician for immediate opening. Moderate volume, income $120,000. Great outdoor activities including fishing, boating, skiing and sailing in south central Washington. Send CV to KEP, PO Box 6192, Kennewick, WA 99336; or call (509) 627-1798.

UNIVERSITY OF CALIFORNIA, Irvine, Department of Medicine is seeking a full-time faculty person as General Internist for expanding academic group practice. Combined fee-for-service/capitation. Duties include 80-90% clinical practice in multispecialty faculty clinic, 10-20% teaching residents and students ambulatory care and inpatient medicine. Division of General Internal Medicine with strong commitment to teaching, practice, and research. Competitive salary and benefits. Affirmative action/equal opportunity employer. Send CV to Jeremiah Tilles, MD, UCI, Department of Medicine, Route 81, 101 City Drive South, Orange, CA 92668.

(Continued on Page 368)

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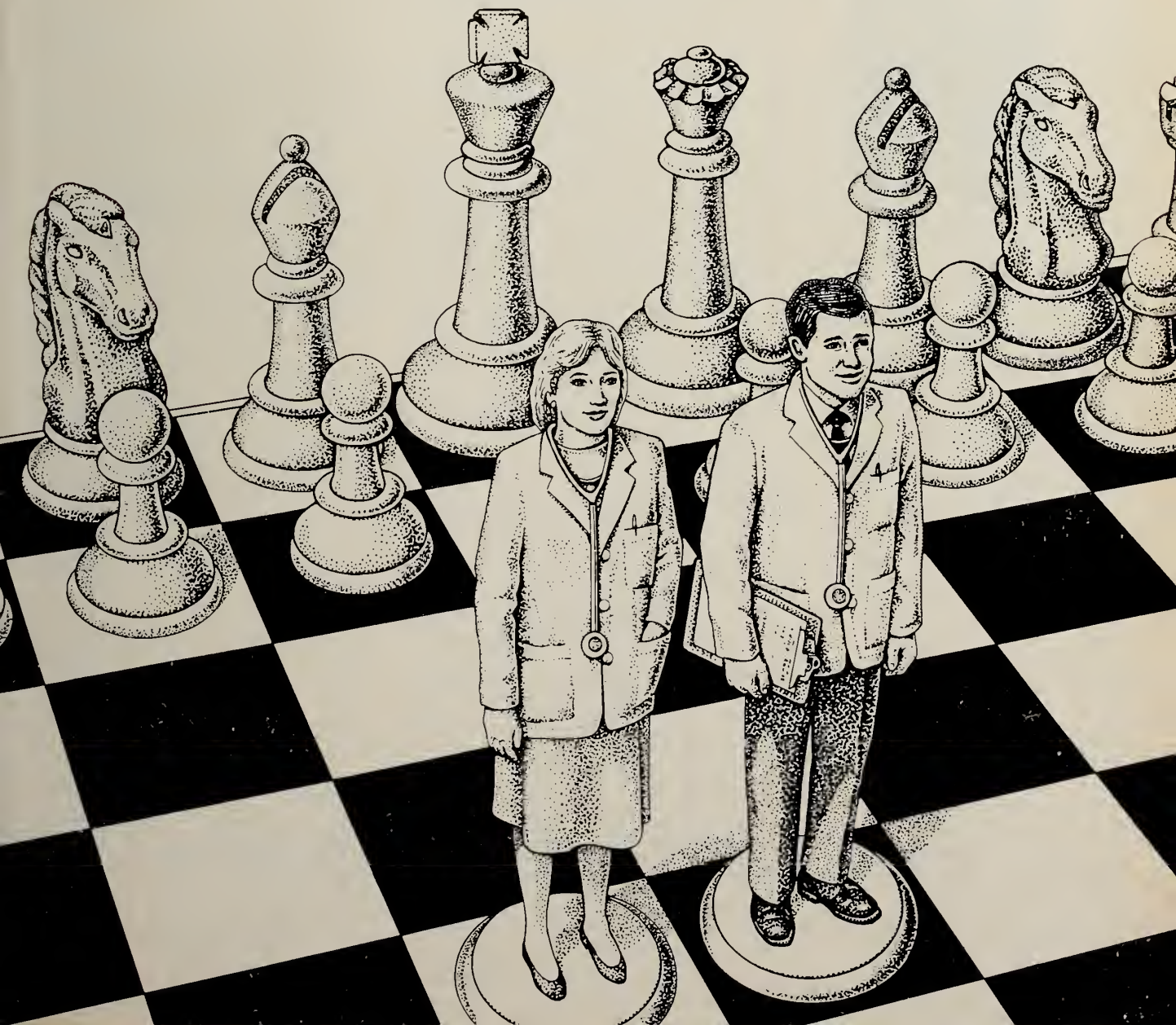

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(Continued from Page 366)

PHYSICIANS WANTED

ORTHOPEDIST. The west coast's leading Occupational/Family Practice medical provider has FT/PT opportunities for Orthopedic Specialists in California and Washington (Seattle/Tacoma). Attractive package includes: guaranteed salary, incentive bonus and benefits. Current license. Contact Personnel Director, ReadiCare, Inc, 446 Oakmead Parkway, Sunnyvale, CA 94086; (800) 237-3234. Join our dynamic team of professionals. Practice and live in an incomparable environment.

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INTERNIST. Immediate opening for a BC/BE General Internist to join a 35-member multispecialty group located in San Luis Obispo on the central coast. Benefits include immediate shareholder status, retirement program, all practice costs paid, starting guaranteed salary plus strong incentive plan. Send CV to Recruitment, San Luis Medical Clinic, Ltd., 1235 Osos St, San Luis Obispo, CA 93401-3619.

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OCCUPATIONAL/FAMILY PRACTICE. Excellent opportunities with the west coast's leading provider of Occupational/Family Practice medicine. Full/part-time positions throughout California and Washington (Seattle/Tacoma). Current license/CPR. Prior outpatient/family practice/industrial-type trauma experience. Attractive salary/incentives/benefits/malpractice. Contact Personnel Director, ReadiCare, Inc, 446 Oakmead Parkway, Sunnyvale, CA 94086; (800) 237-3234. Join our dynamic team of professionals. Practice and live in an incomparable environment.

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PHYSICIANS WANTED. A General Surgeon and an Oncologist to join 16 physician multispecialty group with attached 40-bed hospital located in southern Idaho. Contact Business Administrator, Box 1233, Twin Falls, ID 83301.

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GENERAL SURGERY. Kaiser Permanente office in central California, rapidly growing new market area, seeking BC/BE specialty physicians in General Surgery. Address inquiries to Larry L. Coble, MD, Kaiser Permanente, 4785 N. First St, Fresno, CA 93726; (209) 221-4825.

ORTHOPEDICS. Kaiser Permanente office in central California, rapidly growing new market area, seeking BC/BE specialty physicians in Orthopedics. Address inquiries to Larry L. Coble, MD, Kaiser Permanente, 4785 N. First St, Fresno, CA 93726; (209) 221-4825.

INTERNAL MEDICINE. San Ysidro Health Center, a comprehensive multispecialty clinic in south San Diego County, seeks an Internist for full-time work. Competitive salary, excellent benefits. Send résumé to Norma Diaz, 4004 Beyer Blvd, San Ysidro, CA 92073; (619) 428-4463 ext 361.

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FAMILY PRACTICE. Rural Colorado. BC/BE Family Practitioner to join three Family Practitioners in growing multispecialty group. Excellent opportunity for person interested in rural living, mountain recreation, health care delivery for medically underserved populations. Send CV to Michael Bloom, 204 Carson Ave, Alamosa, CO 81101; (303) 589-5161.

WALK-IN PHYSICIAN WANTED. ER/Primary Care training preferred, outstanding opportunity to start new department in rapidly growing multispecialty fee-for-service clinic in east San Gabriel Valley. Excellent salary and incentives. Send CV to Mr Ghormley. Administrator, 420 W. Rowland, Covina, CA 91723.

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PEDIATRICIAN position available with multispecialty group; BE/BC required; strong incentive plan; benefits included; retirement program and located in San Luis Obispo, California on the central coast. Send CV to Administration/Recruitment, San Luis Medical Clinic, 1235 Osos St, San Luis Obispo, CA 93401.

OBSTETRICS/GYNECOLOGY. Kaiser Permanente office in central California, rapidly growing new market area, seeking BC/BE specialty physicians in OB/GYN. Address inquiries to Larry L. Coble, MD, Kaiser Permanente, 4785 N. First St, Fresno, CA 93726; (209) 221-4825.

PHYSICIANS WANTED

FAMILY PRACTITIONER. San Ysidro Health Center, a comprehensive multispecialty clinic in south San Diego County, seeks a Family Practitioner for full-time work. Competitive salary, excellent benefits. Send résumé to Norma Diaz, 4004 Beyer Blvd, San Ysidro, CA 92073; (619) 428-4463 ext 361.

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GASTROENTEROLOGIST position available with multispecialty group; BE/BC required; strong incentive plan; benefits included; retirement program and located in San Luis Obispo, California on the central coast. Send CV to Administration/Recruitment, San Luis Medical Clinic, 1235 Osos St, San Luis Obispo, CA 93401.

INTERNIST/NEPHROLOGIST with special interest in teaching Internal Medicine for full-time appointment in university-affiliated, active teaching and clinical program with part-time Nephrology private practice. Inquiries, including CV, should be sent to M.B. Ross, MD, Chairman, Department of Medicine, San Bernardino County Medical Center, 780 E. Gilbert St, San Bernardino, CA 92404.

PHYSICIANS WANTED

DERMATOLOGY. Kaiser Permanente office in central California, rapidly growing new market area, seeking BC/BE specialty physicians in Dermatology. Address inquiries to Larry L. Coble, MD, Kaiser Permanente, 4785 N. First St, Fresno, CA 93726; (209) 221-4825.

FAMILY PRACTITIONER position available with multispecialty group; BE/BC required; strong incentive plan; benefits included; retirement program and located in San Luis Obispo, California on the central coast. Send CV to Administration/Recruitment, San Luis Medical Clinic, 1235 Osos St, San Luis Obispo, CA 93401.

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PHYSICIANS NEEDED for immediate employment in non-surgical hemorrhoid treatment facility. 30 hours per week. Attractive salary package. Send résumé to Dr G. Green, PO Box 12565-W, Reno, NV 89510-2565.

RADIOLOGIST needed part-time to read office x-rays for large musculoskeletal group in Sacramento, California. Fees negotiable. Send CV to Number 90, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

ORTHOPEDIC SURGEONS, BE/BC, general ortho or with spine, knee, hand, sports medicine fellowship, wanted for immediate openings in Sacramento, California, musculoskeletal specialty group. Guarantee, malpractice insurance, vacation first year, fee-for-service thereafter plus partnership opportunity. Interested physicians send CV to Number 91, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

THE UNIVERSITY OF WASHINGTON seeks Assistant Professor in Nephrology to establish independent research program in molecular biology of renal diseases. Must be BC in Internal Medicine and BC/BE in Nephrology, qualified to provide clinical care and teach in Internal Medicine and Nephrology, trained for three plus years in renal cell biology with molecular biology experience and have independent grant or career development award. The University of Washington is an EOE. Please reply to Number 88, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

FAMILY PHYSICIAN. BC/BE to join the Family Practice department of a busy, primary care based multispecialty group. Excellent opportunity for growth. Contact Shane Spray, Administrator, Skagit Valley Medical Center, 1400 E. Kincaid, Mt. Vernon, WA 98273; (206) 428-2524.

(Continued on Page 376)

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References: 1. Newton RE, *et al* A review of the side effect profile of buspirone *Am J Med* 1986,80(3B) 17-21 2. Moskowitz H and Smiley A Effects of chronically administered buspirone and diazepam on driving-related skills performance *J Clin Psychiatry* 1982 43(12,Sec 2) 45-55 3. Lader M Assessing the potential for buspirone dependence or abuse and effects of its withdrawal *Am J Med* 1987,82(5A) 20-26

Contraindications: Hypersensitivity to buspirone.

Warnings: The administration of BuSpar to a patient taking a monoamine oxidase inhibitor (MAOI) may pose a hazard. Since blood pressure has become elevated when BuSpar was administered concomitantly with an MAOI, such concomitant use is not recommended BuSpar should not be employed in lieu of appropriate antipsychotic treatment

Precautions: ***General***—*Interference with cognitive and motor performance.* Although buspirone is less sedating than other anxiolytics and does not produce significant functional impairment, its CNS effects in a given patient may not be predictable, therefore, patients should be cautioned about operating an automobile or using complex machinery until they are reasonably certain that buspirone does not affect them adversely Although buspirone has not been shown to increase alcohol-induced impairment in motor and mental performance, it is prudent to avoid concomitant use with alcohol.

Potential for withdrawal reactions in sedative/hypnotic/anxiolytic drug dependent patients. Because buspirone will not block the withdrawal syndrome often seen with cessation of therapy with benzodiazepines and other common sedative/hypnotic drugs, before starting buspirone withdraw patients gradually from their prior treatment, especially those who used a CNS depressant chronically Rebound or withdrawal symptoms may occur over varying time periods, depending in part on the type of drug and its elimination half-life. The withdrawal syndrome can appear as any combination of irritability, anxiety agitation, insomnia, tremor, abdominal cramps, muscle cramps, vomiting, sweating, flu-like symptoms without fever, and occasionally, even as seizures.

Possible concerns related to buspirone's binding to dopamine receptors. Because buspirone can bind to central dopamine receptors, a question has been raised about its potential to cause acute and chronic changes in dopamine mediated neurological function (e.g., dystonia, pseudoparkinsonism, akathisia, and tardive dyskinesia) Clinical experience in controlled trials has failed to identify any significant neuroleptic-like activity; however, a syndrome of restlessness, appearing shortly after initiation of treatment, has been reported, the syndrome may be due to increased central noradrenergic activity or may be attributable to dopaminergic effects (ie, represent akathisia).

Information for Patients—Patients should be instructed to inform their physician about any medications, prescription or non-prescription, alcohol or drugs they are now taking or plan to take during treatment with buspirone; to inform their physician if they are pregnant, are planning to become pregnant, or become pregnant while taking buspirone; to inform their physician if they are breast feeding, and not to drive a car or operate potentially dangerous machinery until they experience how this medication affects them

Drug Interactions—Concomitant use with other CNS active drugs should be approached with caution (see **Warnings**). Concomitant use with trazodone may have caused 3- to 6-fold elevations on SGPT (ALT) in a few patients. Buspirone does not displace tightly bound drugs like phenytoin, propranolol, and warfarin from serum proteins, but may displace less firmly bound drugs like digoxin.

Carcinogenesis, Mutagenesis, Impairment of Fertility—No evidence of carcinogenic potential was observed in rats or mice; buspirone did not induce point mutations, nor was DNA damage observed, chromosomal aberrations or abnormalities did not occur.

Pregnancy: Teratogenic Effects—Pregnancy Category B. Should be used during pregnancy only if clearly needed.

Nursing Mothers—Administration to nursing women should be avoided if clinically possible.

Pediatric Use—The safety and effectiveness have not been determined in individuals below 18 years of age

Use in the Elderly—No unusual, adverse, age-related phenomena have been identified in elderly patients receiving a total, modal daily dose of 15 mg.

Use in Patients with Impaired Hepatic or Renal Function—Since buspirone is metabolized by the liver and excreted by the kidneys, it is not recommended in severe hepatic or renal impairment

Adverse Reactions (See also Precautions): ***Commonly Observed***—The more commonly observed untoward events include dizziness, nausea, headache, nervousness, lightheadedness, and excitement.

Associated with Discontinuation of Treatment—The more common events causing discontinuation included central nervous system disturbances (3 4%), primarily dizziness, insomnia, nervousness, drowsiness, lightheaded feeling; gastrointestinal disturbances (1.2%), primarily nausea, miscellaneous disturbances (1.1%), primarily headache and fatigue. In addition, 3.4% of patients had multiple complaints, none of which could be characterized as primary

Incidence in Controlled Clinical Trials—Adverse events reported by 1% or more of 477 patients who received buspirone in four-week, controlled trials: *Cardiovascular:* Tachycardia/palpitations 1%. *CNS:* Dizziness 12%, drowsiness 10%, nervousness 5%, insomnia 3%, lightheadedness 3%, decreased concentration 2%, excitement 2%, anger/hostility 2%, confusion 2%, depression 2% *EENT.* Blurred vision 2% *Gastrointestinal.* Nausea 8%, dry mouth 3%, abdominal/gastric distress 2%, diarrhea 2%, constipation 1%, vomiting 1% *Musculoskeletal.* Musculoskeletal aches/pains 1% *Neurological:* Numbness 2%, paresthesia 1%, incoordination 1%, tremor 1%. *Skin.* Skin rash 1%. *Miscellaneous* Headache 6%, fatigue 4%, weakness 2%, sweating/clamminess 1%.

Other Events Observed During the Entire Pre-marketing Evaluation—The relative frequency of all other undesirable events reasonably associated with the use of buspirone in approximately 3000 subjects who took multiple doses of the drug under well-controlled, open, and uncontrolled conditions is defined as follows: Frequent are those occurring in at least 1/100 patients; infrequent are those occurring in 1/100 to 1/1000 patients; and rare are those occurring in less than 1/1000 patients *Cardiovascular*—frequent. nonspecific chest pain; infrequent: syncope, hypotension, hypertension, rare: cerebrovascular accident, congestive heart failure, myocardial infarction, cardiomyopathy, bradycardia *Central Nervous System*—frequent. dream disturbances, infrequent depersonalization, dysphoria, noise intolerance, euphoria, akathisia, fearfulness, loss of interest, disassociative reaction, hallucinations, suicidal ideation, seizures, rare: feelings of claustrophobia, cold intolerance, stupor, slurred speech, psychosis *EENT*—frequent. tinnitus, sore throat, nasal congestion; infrequent redness and itching of the eyes, altered taste, altered smell, conjunctivitis; rare: inner ear abnormality, eye pain, photophobia, pressure on eyes *Endocrine*—rare: galactorrhea, thyroid abnormality *Gastrointestinal*—infrequent. flatulence, anorexia, increased appetite, salivation, irritable colon, rectal bleeding; rare: burning of the tongue *Genitourinary*—infrequent. urinary frequency, urinary hesitancy, menstrual irregularity and spotting, dysuria; rare: amenorrhea, pelvic inflammatory disease, enuresis, nocturia *Musculoskeletal*—infrequent: muscle cramps, muscle spasms, rigid/stiff muscles, arthralgias. *Neurological*—infrequent: involuntary movements, slowed reaction time; rare: muscle weakness. *Respiratory*—infrequent. hyperventilation, shortness of breath, chest congestion; rare: epistaxis *Sexual Function*—infrequent: decreased or increased libido, rare. delayed ejaculation, impotence. *Skin*—infrequent edema, pruritus, flushing, easy bruising, hair loss, dry skin, facial edema, blisters; rare: acne, thinning of nails. *Clinical Laboratory*—infrequent: increases in hepatic aminotransferases (SGOT, SGPT); rare eosinophilia, leukopenia, thrombocytopenia *Miscellaneous*—infrequent weight gain, fever, roaring sensation in the head, weight loss, malaise; rare: alcohol abuse, bleeding disturbance, loss of voice, hiccoughs

Drug Abuse and Dependence: ***Controlled Substance Class***—Not a controlled substance.

Physical and Psychological Dependence—Buspirone has shown no potential for abuse or diversion and there is no evidence that it causes tolerance, or either physical or psychological dependence. However, since it is difficult to predict from experiments the extent to which a CNS active drug will be misused, diverted, and/or abused once marketed, physicians should carefully evaluate patients for a history of drug abuse and follow such patients closely, observing them for signs of buspirone misuse or abuse (e.g., development of tolerance, incrementation of dose, drug-seeking behavior).

Overdosage: ***Signs and Symptoms***—At doses approaching 375 mg/day the following symptoms were observed nausea, vomiting, dizziness, drowsiness, miosis, and gastric distress. No deaths have been reported in humans either with deliberate or accidental overdosage.

Recommended Overdose Treatment—General symptomatic and supportive measures should be used along with immediate gastric lavage. No specific antidote is known and dialyzability of buspirone has not been determined.

For complete details, see Prescribing Information or consult your Mead Johnson Pharmaceuticals Representative

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CONTINUING MEDICAL EDUCATION

(Continued from Page 364)

July 15-18—**Caring for People With AIDS and Their Loved Ones.** Concern for Dying: an Educational Council, at Bishop's Ranch, Healdsburg. Fri-Mon. Contact: Penny Weingarten, 250 West 57th St., Room 831, New York, NY 10107. (800) 248-2122.

July 27-31—**Wilderness Medicine '88.** Wilderness Medical Society at Squaw Valley, Lake Tahoe. Wed-Sun. 22 hrs. Contact: Jackie Silva, Coordinator, Mountain Medical Seminars, PO Box 321, Yreka, 96097. (916) 842-4667.

August 3-6—**15th Annual Meeting: The Peruvian American Medical Society** at Westin Bonaventure Hotel, Los Angeles. Wed-Sat. Contact: Hugo Ortiz, MD, Chairman, Scientific Program, 6488 Tamerlane Dr, West Bloomfield, MI 48322.

September 15-18—**Decentralized Care of People With AIDS: An Educational Seminar for Developmental Approach.** Sonoma County Academic Foundation for Excellence at Flamingo Hotel, Santa Rosa. Thurs-Sun. $275. Contact: Mary Ellen Buechter, SCAFE, 3325 Chanate Rd, Santa Rosa, 95404. (707) 527-4121.

IDAHO

March 12-19—**Strategies for Fitness and Health Promotion.** University of Arizona College of Medicine, Department of Family and Community Medicine, and Epic Expeditions at Sun Valley. One week. 24 hrs. Contact: Kathy Rairigh, PO Box 209, Sun Valley 83353. (208) 788-4995.

March 17-18—**Idaho Thoracic Society—Annual Medical Symposium.** Anderson Center, Boise. Contact: Idaho Thoracic Society, 2621 Camas St, Boise 83705. (208) 344-6567.

July 21-23—**Idaho Medical Association Annual Meeting.** Sun Valley. Thurs-Sat. Contact: IMA, 305 W. Jefferson, PO Box 2668, Boise 83701. (208) 344-7888.

MONTANA

September 29-October 1—**Montana Medical Association Annual Meeting.** Heritage Inn, Great Falls. Fri-Sat. Contact: MMA, 2012 11th Ave., Suite 12, Helena 59601. (406) 443-4000.

NEW MEXICO

Information, requests for accreditation and items to be listed should be sent to the chairman of the CME Committee, New Mexico Medical Society, 303 San Mateo NE, Suite 204, Albuquerque, NM 87108 at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 266-7868.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

April 21-23—**10th Annual Pediatric Cardio-Pulmonary Update.** Sheraton Old Town, Albuquerque. Contact: UNM SOM, Office of CME, (505) 277-3942.

April 29-May 1—**Southwest Allergy Forum.** Eldorado Hotel, Sante Fe. Contact: UNM SOM, Office of CME, (505) 277-3942.

(Continued on Page 380)

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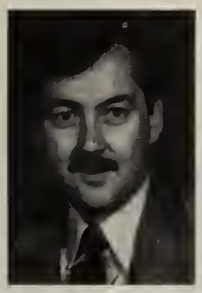

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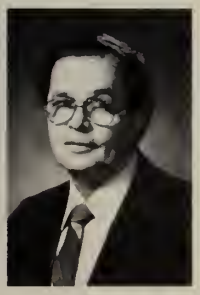

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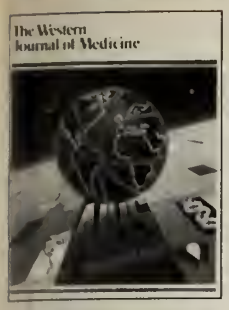

AIDS—A Global Perspective

The short and remarkable history of AIDS epidemiology began in 1981 with the description of the clinical syndrome in California and New York. In the 6 years that have followed, intensive epidemiologic studies have defined the mode of spread of AIDS and laid the foundation for current control efforts. Serosurveys and retrospective clinical studies have been used to trace the temporal origins of the pandemic prior to 1981, while prospective studies and an increasingly comprehensive worldwide surveillance system have provided more accurate data for the years following 1981. AIDS cases have now been reported and investigated throughout the world.

This issue, from the Special Programme on AIDS of the World Health Organization, considers the methods and limitations of AIDS case reporting and HIV serologic studies, summarizes modes of HIV transmission, defines geographic patterns of spread, and examines the epidemiology of HIV infections by continent.

—Jonathan M. Mann, MD
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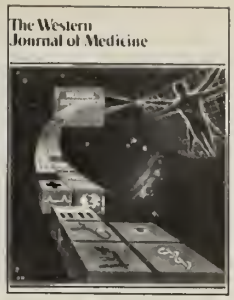

Medical Informatics

I would suggest that the computer in its relation to medicine is analogous to that of the microscope in the last century. . . . The analogous role that I believe the computer is now taking on is also that of a breakthrough tool—one enabling us to explore and better understand the informational and cognitive foundations of medicine. Its application to the classification and retrieval of data and to the management of information will result in a deeper insight into the structure of medical information and knowledge itself.

—Marsden S. Blois, PhD, MD

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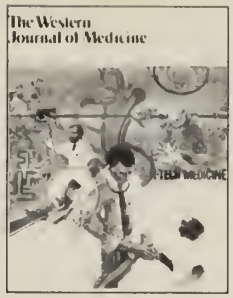

High-Tech Medicine

Progress in medical science seems to come in rushes. There are long periods of time during which we mainly fine-tune the status quo: third-generation drugs, better optics for endoscopes, more accurate assays, rapid development of x-ray film and so forth. Then, out of nowhere, a surge of new discoveries whose potential applications to medical practice seem limitless takes our breath away. We are now in such an epoch. Powerful and precise lasers. Almost unbelievable organ transplantation. Complex and uniquely informative magnetic resonance imaging and positron emission tomography. Exquisitely specific monoclonal antibodies. And the immense potential of modern molecular biology. This rush of new advances, collapsed into such a brief period of time, boggles the mind.

—R. Paul Robertson, MD

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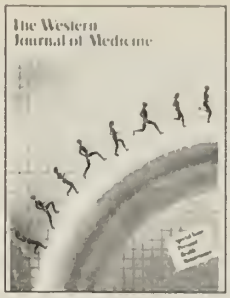

Personal Health Maintenance

The goal of this special issue is to provide an authoritative, current guide to disease prevention and health promotion. The contributors are distinguished experts in public health, epidemiology and clinical medicine.

—John H. Holbrook, MD

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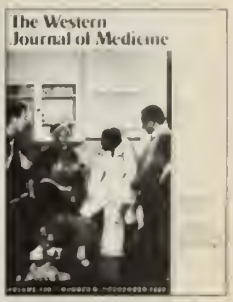

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—Malcolm S.M. Watts, MD

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(Continued from Page 370)

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CAMARILLO (Ventura County). Multispecialty group of 35 physicians has immediate positions available for BC/BE Family Practitioner. This opening is located in the Camarillo satellite with the main facility located in Ventura. The growth oriented group is located on the California coast, 60 miles north of Los Angeles. Guaranteed salary plus incentives. No investment required. City is a great place to raise a family in a clean environment. Send résumé to Recruitment, Family Practice, 2705 Loma Vista Rd, Ventura, CA 93003.

VENTURA (Ventura County). Multispecialty group of 35 physicians has immediate position available for BC/BE Family Practitioner. This opening is located in the Immediate Care department. The growth oriented group is located on the California coast, 60 miles north of Los Angeles. Guaranteed salary plus incentives. No investment required. City is a great place to raise a family in a clean environment. Send résumé to Recruitment, Family Practice, 2705 Loma Vista Rd, Ventura, CA 93003.

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LOS ANGELES. Part-time. Busy Occupational/Urgent Care Clinic seeks EM/FP caring professional 24-32 hours per week. Competitive compensation. Ted Angus, MD, 10720 So. Paramount Blvd, Downey, CA 90241.

FAMILY PHYSICIAN needed in northern New Mexico. Prime opportunity for BE/BC Family Physician looking for a challenge. Contact NM Health Resources, PO Box 27650, Albuquerque, NM 87125; (505) 242-0633.

PEDIATRICIAN. Large multispecialty group in San Francisco bay area seeks BC/BE full-time Pediatrician to join a growing practice. Attractive salary and benefits. Send CV to Fremont Medical Clinic, 39111 Paseo Padre Parkway, Ste 203, Fremont, CA 94538; Attention: Joy.

CALIFORNIA MOUNTAINS. Family Practice, community of 5,000 people needs a Family Physician to join the staff of their 26-bed acute care facility, full range of practice, income potential in the 100's, rural atmosphere in the scenic Sierra Nevada Mountains. For more information call David King collect at (714) 548-0220 or send CV to 500 N. Newport Blvd, Ste 204, Newport Beach, CA 92663.

FAMILY PHYSICIAN. UTAH IS BLOOMING—DISCOVER IT. Multispecialty practice currently has a position for a BC/BE Family Physician to join established group (three Family Practitioners, OB, two Pediatricians, General Surgeon); 35 miles/45 minutes from Salt Lake City; income guaranteed/excellent benefits; excellent outdoor recreational opportunities. Contact Dorothy Leonelli, Administrator, Family Practice Group, 255 South First East, Tooele, UT 84074; (801) 882-0424.

PEDIATRICIAN, BC/BE. Interest in Neonatology preferred. Attractive salary and benefits. Partnership available in two years. Busy practice in agricultural community one-and-one-half hours from San Diego, California. Reply with CV to Drs Mirza R. Baig and Mohammad I. Admani, PO Box 590, El Centro, CA 92243.

FAMILY PRACTITIONER needed for multispecialty group of 27 physicians in town of 25,000 in agricultural area 20 miles from state capitol. Clinic adjacent to 150-bed hospital. $70,000 guarantee plus bonus first year. Full stockholder status thereafter plus many fringe benefits. Close to excellent outdoor recreational activities. Contact Mike Crane, 215 E. Hawaii, Nampa, ID 83651; (208) 467-1121.

BEAUTIFUL MONTEREY BAY. Immediate opportunity for a friendly, skilled, Family Practice or Emergency Physician to join highly respected urgent care group with two beautiful Santa Cruz clinics. Committed to high quality care. Nice people, flexible scheduling, comprehensive benefits, including: paid malpractice, group health insurance, long-term disability insurance, no nights, rapid advancement to full partnership in an outstanding place to live. Please send CV to Robert Korns, MD, 6800 Soquel Dr, Aptos, CA 95003 or call (408) 662-3611.

PHYSICIANS WANTED

OVERSEAS OPPORTUNITY

New Private Hospitals in Riyadh and Jeddah, Saudi Arabia are recruiting physicians, dentists, and administrators for one-two year and three month appointments.

Positions available include:

General Internist	Orthopedics
Pediatrics	Psychiatry
General Surgery	Urology
Obstetrics/ Gynecology	Medical Director
Anesthesiology	General Dentistry
Cardiology	Orthodenture
Dermatology	Physiatry
Endocrinology	Hospital Director
Neurology	Director of Nurses
Neurosurgery	
Ophthalmology	

Excellent compensation and benefits including free housing, school tuition for children and major tax savings for one year and over appointments. Minimum of three years professional experience required.

Send résumé or call:

Roger Bennett or Peter House
701 Dexter N. #306
Seattle, WA 98109
(206) 286-1334

MEDICAL COORDINATOR FOR LIVER TRANSPLANTATION. The University of California in San Francisco is recruiting for an Assistant or Associate Professor of Clinical Medicine responsible for coordinating medical aspects of liver transplantation program including: preoperative evaluation of prospective recipients; liaison with other medical specialties and supporting services; medical aspects of postoperative care. Candidates should be at least one year beyond completion of training in Gastroenterology, certified by the Board of Internal Medicine in both Medicine and Gastroenterology, provide tangible evidence of clinical, teaching and research accomplishment, and demonstrate personal characteristics necessary for effective interaction in a multidisciplinary environment. Rank and salary will be commensurate with qualifications. Interested individuals should reply to Robert K. Ockner, MD, Division of Gastroenterology, Box 0538, University of California, San Francisco, CA 94143. UCSF is an Equal Opportunity/Affirmative Action employer. Women and minorities are encouraged to apply.

WESTERN MONTANA FAMILY PRACTICE. Family Practitioner seeks associate for busy office practice. Small town near regional hospitals. Surgery assists, no OB. Excellent climate, recreation, and schools. Résumé and inquiries to Number 95, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

IDAHO. Enjoy the great outdoors and an active, interesting Family Practice, including Obstetrics. Join four physicians and nine nurse practitioners working in rural community health centers near Boise. Emphasis on prevention. Good specialist back-up. Available now. Contact Erwin Teuber, Administrator, or Peter Barnett, MD, Medical Director, Terry Reilly Health Services, 211 16th Avenue North, Nampa, ID 83651; (208) 467-4431.

(Continued on Page 381)

First hundreds...

Then thousands...

Soon more than a million.

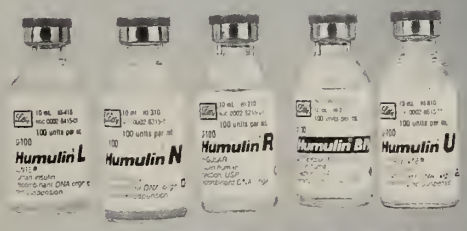
Soon more than a million insulin users will be taking Humulin.

And no wonder. Humulin is identical to the insulin produced by the human pancreas—except that it is made by rDNA technology.

Humulin is not derived from animal pancreases. So it contains none of the animal-source pancreatic impurities that may contribute to insulin allergies or immunogenicity.

The clinical significance of insulin antibodies in the complications of diabetes is uncertain at this time. However, high antibody titers have been shown to decrease the small amounts of endogenous insulin secretion some insulin users still have. The lower immunogenicity of Humulin has been shown to result in lower insulin antibody titers; thus, Humulin may help to prolong endogenous insulin production in some patients.

Any change of insulin should be made cautiously and only under medical supervision. Changes in refinement, purity, strength, brand (manufacturer), type (regular, NPH, Lente®, etc), species/source (beef, pork, beef-pork, or human), and/or method of manufacture (recombinant DNA versus animal-source insulin) may result in the need for a change in dosage.



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Humulin®
human insulin
(recombinant DNA origin)

For your insulin-using patients

Lilly Leadership
IN DIABETES CARE

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Eli Lilly and Company
Indianapolis, Indiana
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WHEN ACID REFLUX ERUPTS

Zantac dramatically lessens pain of acid reflux[1] by inhibiting the formation of acid at its source–an action unique among pharmaceutical agents indicated for the treatment of gastroesophageal reflux disease.

Zantac® *Tablets*

ranitidine HCl/Glaxo 150 mg tablets bid

The only H_2-antagonist indicated for the treatment of gastroesophageal reflux disease

1. Sontag S. Robinson M. McCallum R. et al: Ranitidine therapy for gastroesophageal reflux disease: Results of a large double-blind trial *Arch Intern Med* 1987. 147:1485-1491.

See next page for Brief Summary of Product Information.

Glaxo/ ROCHE

ZANTAC® 150 Tablets
(ranitidine hydrochloride)
ZANTAC® 300 Tablets
(ranitidine hydrochloride)

BRIEF SUMMARY

The following is a brief summary only. Before prescribing, see complete prescribing information in ZANTAC® product labeling.

INDICATIONS AND USAGE: ZANTAC® is indicated in:
1. Short-term treatment of **active duodenal ulcer.** Most patients heal within four weeks.
2. **Maintenance therapy** for duodenal ulcer patients at reduced dosage after healing of acute ulcers.
3. The treatment of **pathological hypersecretory conditions** (eg, Zollinger-Ellison syndrome and systemic mastocytosis).
4. Short-term treatment of **active, benign gastric ulcer.** Most patients heal within six weeks and the usefulness of further treatment has not been demonstrated.
5. Treatment of **gastroesophageal reflux disease (GERD).** Symptomatic relief commonly occurs within one or two weeks after starting therapy. Therapy for longer than six weeks has not been studied.

In active duodenal ulcer, active, benign gastric ulcer, hypersecretory states, and GERD, concomitant antacids should be given as needed for relief of pain.

CONTRAINDICATIONS. ZANTAC® is contraindicated for patients known to have hypersensitivity to the drug.

PRECAUTIONS: General: 1. Symptomatic response to ZANTAC® therapy does not preclude the presence of gastric malignancy.

2. Since ZANTAC is excreted primarily by the kidney, dosage should be adjusted in patients with impaired renal function (see **DOSAGE AND ADMINISTRATION**). Caution should be observed in patients with hepatic dysfunction since ZANTAC is metabolized in the liver.

Laboratory Tests: False-positive tests for urine protein with Multistix® may occur during ZANTAC therapy, and therefore testing with sulfosalicylic acid is recommended.

Drug Interactions: Although ZANTAC has been reported to bind weakly to cytochrome P-450 in vitro, recommended doses of the drug do not inhibit the action of the cytochrome P-450-linked oxygenase enzymes in the liver. However, there have been isolated reports of drug interactions which suggest that ZANTAC may affect the bioavailability of certain drugs by some mechanism as yet unidentified (eg, a pH-dependent effect on absorption or a change in volume of distribution).

Carcinogenesis, Mutagenesis, Impairment of Fertility: There was no indication of tumorigenic or carcinogenic effects in lifespan studies in mice and rats at doses up to 2,000 mg/kg/day.

Ranitidine was not mutagenic in standard bacterial tests (*Salmonella, E coli*) for mutagenicity at concentrations up to the maximum recommended for these assays.

In a dominant lethal assay, a single oral dose of 1,000 mg/kg to male rats was without effect on the outcome of two matings per week for the next nine weeks.

Pregnancy: ***Teratogenic Effects: Pregnancy Category B:*** Reproduction studies have been performed in rats and rabbits at doses up to 160 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to ZANTAC. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers: ZANTAC is secreted in human milk. Caution should be exercised when ZANTAC is administered to a nursing mother.

Pediatric Use: Safety and effectiveness in children have not been established.

Use in Elderly Patients: Ulcer healing rates in elderly patients (65 to 82 years of age) were no different from those in younger age groups. The incidence rates for adverse events and laboratory abnormalities were also not different from those seen in other age groups.

ADVERSE REACTIONS: The following have been reported as events in clinical trials or in the routine management of patients treated with oral ZANTAC.* The relationship to ZANTAC therapy has been unclear in many cases. Headache, sometimes severe, seems to be related to ZANTAC administration.

Central Nervous System: Rarely, malaise, dizziness, somnolence, insomnia, and vertigo. Rare cases of reversible mental confusion, agitation, depression, and hallucinations have been reported, predominantly in severely ill elderly patients. Rare cases of reversible blurred vision suggestive of a change in accommodation have been reported.

Cardiovascular: Rare reports of tachycardia, bradycardia, and premature ventricular beats.

Gastrointestinal: Constipation, diarrhea, nausea/vomiting, and abdominal discomfort/pain.

Hepatic: In normal volunteers, SGPT values were increased to at least twice the pretreatment levels in 6 of 12 subjects receiving 100 mg qid IV for seven days, and in 4 of 24 subjects receiving 50 mg qid IV for five days. With oral administration there have been occasional reports of reversible hepatitis, hepatocellular or hepatocanalicular or mixed, with or without jaundice.

Musculoskeletal: Rare reports of arthralgias.

Hematologic: Reversible blood count changes (leukopenia, granulocytopenia, thrombocytopenia) have occurred in a few patients. Rare cases of agranulocytosis or of pancytopenia, sometimes with marrow hypoplasia, have been reported.

Endocrine: Controlled studies in animals and man have shown no stimulation of any pituitary hormone by ZANTAC (ranitidine hydrochloride) and no antiandrogenic activity, and cimetidine-induced gynecomastia and impotence in hypersecretory patients have resolved when ZANTAC has been substituted. However, occasional cases of gynecomastia, impotence, and loss of libido have been reported in male patients receiving ZANTAC, but the incidence did not differ from that in the general population.

Integumentary: Rash, including rare cases suggestive of mild erythema multiforme, and rarely, alopecia.

Other: Rare cases of hypersensitivity reactions (eg, bronchospasm, fever, rash, eosinophilia) and small increases in serum creatinine.

OVERDOSAGE: Information concerning possible overdosage and its treatment appears in the full prescribing information.

DOSAGE AND ADMINISTRATION: Active Duodenal Ulcer: The current recommended adult oral dosage is 150 mg twice daily. An alternate dosage of 300 mg once daily at bedtime can be used for patients in whom dosing convenience is important. The advantages of one treatment regimen compared to the other in a particular patient population have yet to be demonstrated.

Maintenance Therapy: The current recommended adult oral dosage is 150 mg at bedtime.

Pathological Hypersecretory Conditions (such as Zollinger-Ellison syndrome): The current recommended adult oral dosage is 150 mg twice a day. In some patients it may be necessary to administer ZANTAC® 150-mg doses more frequently. Doses should be adjusted to individual patient needs, and should continue as long as clinically indicated. Doses up to 6 g/day have been employed in patients with severe disease.

Benign Gastric Ulcer: The current recommended adult oral dosage is 150 mg twice a day.

GERD: The current recommended adult oral dosage is 150 mg twice a day.

Dosage Adjustment for Patients with Impaired Renal Function: On the basis of experience with a group of subjects with severely impaired renal function treated with ZANTAC, the recommended dosage in patients with a creatinine clearance less than 50 ml/min is 150 mg every 24 hours. Should the patient's condition require, the frequency of dosing may be increased to every 12 hours or even further with caution. Hemodialysis reduces the level of circulating ranitidine. Ideally, the dosage schedule should be adjusted so that the timing of a scheduled dose coincides with the end of hemodialysis.

HOW SUPPLIED: ZANTAC® 300 Tablets (ranitidine hydrochloride equivalent to 300 mg of ranitidine) are yellow, capsule-shaped tablets embossed with "ZANTAC 300" on one side and "Glaxo" on the other. They are available in bottles of 30 (NDC 0173-0393-40) and unit dose packs of 100 tablets (NDC 0173-0393-47).

ZANTAC® 150 Tablets (ranitidine hydrochloride equivalent to 150 mg of ranitidine) are white tablets embossed with "ZANTAC 150" on one side and "Glaxo" on the other. They are available in bottles of 60 tablets (NDC 0173-0344-42) and unit dose packs of 100 tablets (NDC 0173-0344-47).

Store between 15° and 30°C (59° and 86°F) in a dry place. Protect from light. Replace cap securely after each opening.

August 1987

Glaxo

Glaxo Inc.
Research Triangle Park, NC 27709

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CONTINUING MEDICAL EDUCATION

(Continued from Page 372)

May 5-7—**NM Medical Society Annual Meeting—AIDS—Reducing the Risk and Chemical Dependency Seminar.** Physicians Mutual Liability Insurance Co **Loss Control Seminar.** Albuquerque Hilton Inn. Contact: New Mexico Medical Society, 303 San Mateo NE, Albuquerque 87108. (505) 266-7868.

May 13—**The Physician in Crisis.** Presbyterian Hospital Quality of Life Committee. Contact: Mary Boning, RN, PO Box 26666, Albuquerque 87125. (505) 841-1225.

May 14—**Cardiac Physical Diagnosis Symposium.** Contact: UNM SOM, Office of CME, (505) 277-3942.

May 19-20—**Mental Health Services With Hispanic and Native American Children and Families.** Contact: UNM SOM, Office of CME, (505) 277-3942.

June 2-3—**8th Annual UNM/ACEP Emergency Medicine Symposium.** AMFAC Hotel, Albuquerque. Contact: UNM SOM, Office of CME, (505) 277-3942.

July 18-21—**Ruidoso Family Practice Seminar.** Inn of the Mountain Gods, Mescalero. Contact: NM Chapter, AAFP, PO Box 23070, Albuquerque 87192. (505) 298-5300.

July 22-24—**Diagnosis and Management of Arrhythmia.** Contact: Presbyterian Heart Institute, Albuquerque, (505) 841-1065/(505) 242-2796.

October 28-29—**New Mexico Medical Society Interim Meeting** and **Loss Control Seminar,** Physicians Mutual Liability Insurance Co. Journal Center Pyramid Holiday Inn, Albuquerque. Contact: New Mexico Medical Society, 303 San Mateo NE, Albuquerque 87108. (505) 266-7868.

UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the CME office of the Utah Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. They also must meet the definition of Utah Approved CME Credit for the purpose of medical license reregistration in Utah. Accredited institutions wishing to list AMA Category 1/Utah Approved CME courses here should send information at least two months in advance to the Office of Continuing Medical Education, 540 East Fifth South, Salt Lake City, Utah 84102; or phone (801) 355-5290. For information on CME accreditation or on the CME requirements of the Utah Physicians' Licensing Board, please write the CME office at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution or the CME office for current details.

MEDICAL GRAND ROUNDS

Each Wed—8:00-9:00 a.m. Alternating between University of Utah Medical Center and VA Medical Center, Salt Lake City. Contact: William D. Odell, MD, PhD, Professor and Chairman, Dept of Internal Medicine, Univ of Utah, (801) 581-7606.

* * *

March 30-April 4—**Common Problems in Pediatrics** (Sponsor: UUMC). Wed-Sun. Contact: K. Blosch, (801) 466-3500.

April 22—**Hypercholesterolemia** (Sponsor: UUMC). Fri. Park Hotel, Salt Lake City. Contact: Rosalie Lammle, (801) 581-8664.

May 5-6—**Ethics and Health: Quality Care in the Age of Cost-consciousness** (Sponsor: UUMC). Thurs-Fri. Union Building, University of Utah. Contact: (801) 581-5705.

July 17-22—**6th Annual Update in Clinical Microbiology and Immunology** (Sponsor: UUMC). Sun-Fri. 25 hours. Jackson Hole, Wyoming. Contact: (801) 581-7408.

August 13-15—**Retrieved Implants and Biomaterials** (Sponsor: UUMC). Fri-Sun. Contact: Rosalie Lammle, (801) 581-8664.

(Continued on Page 382)

(Continued from Page 376)

PHYSICIANS WANTED

Physicians wanted for leading clinic

Prestigious Chicago-based clinic group specializing in the treatment of venous disorders is expanding nationally. Our newest clinics in Los Angeles, San Francisco, Seattle, San Diego and Phoenix are in need of physicians trained in internal medicine—or who have a broad base of medical experience. We will provide complete training in the latest proprietary techniques of treating venous disorders. We offer a six figure salary and bonus potential, along with malpractice insurance and health benefits. And since there are no weekend hours and a 40-hour work week, you will have plenty of leisure time. You won't have to worry about soliciting for patients or fighting insurance companies.

This is an outstanding opportunity for professional and financial advancement. If you are motivated to build a rewarding practice with the leader in the treatment of venous disorders, send your resume to:

Medical Director

Vein Clinics of America

2340 S. Arlington Heights Road
Arlington Heights, Illinois 60005

PACIFIC NORTHWEST

Internal Medicine and Family Practice Openings

Immediate and mid-1988 positions available for BC/BE Internal Medicine and Family Practice physicians. Due to rapid program expansion, we are seeking candidates for 3- to 12-month locum tenens and regular, full-time staff positions.

Northwest Permanente, PC, is affiliated with the Kaiser Permanente program in Oregon and Washington. Kaiser Permanente is the oldest and largest HMO of its kind in the country, with programs in 15 states and the District of Columbia. In this region we have over 310,000 enrolled members, two hospitals and 11 outpatient facilities located primarily in the Portland area. Northwest Permanente is a professional corporation of 370 physicians who contract exclusively to provide care for the members of Kaiser Permanente. We provide a stimulating professional environment, a quality lifestyle in the Pacific Northwest, and an attractive salary and benefit package.

If you would like to pursue one of the above positions, please forward your CV and letter of inquiry for an immediate response to

Fred Nomura, MD
Regional Medical Director
Northwest Permanente, PC
3600 N. Interstate Ave
Portland, OR 97227

PHYSICIANS WANTED

ESTABLISHED BC FAMILY PRACTITIONER in south central Washington seeks BE/BC associate with OB interest. Practice in rural, family-oriented community serving area of 45,000. Income guarantee and assistance with relocation. Ski at White Pass. Fishing and other water sports on nearby Rimrock Lake and Columbia River. Contact PROSEARCH, 305 NE 102nd Ave, Portland, OR 97220; (503) 256-2070, ext 202.

SOUTH CENTRAL WASHINGTON COMMUNITY seeks BE/BC Internist for solo practice. Share office space with two other physicians. First year income guarantee and other assistance. Great income potential for right candidate! Progressive 38-bed hospital has CT services. Excellent schools and recreation. Contact PROSEARCH, 305 NE 102nd Ave, Portland, OR 97220; (503) 256-4488.

EXCELLENT TEXAS OPPORTUNITIES. Cardiology, Cardiovascular Surgery, Family Practice, General Surgery, Internal Medicine, OB/GYN, Occupational Medicine, Oncology, Orthopedic Surgery, Otolaryngology, Pediatrics, Pulmonary, Urology. Excellent quality of life, first year guarantee, etc. Other Texas opportunities available also. Reply with CV or call Armando L. Frezza, Medical Support Services, 8806 Balcones Club Dr, Austin, TX 78750; (512) 331-4164.

SOUTHERN CALIFORNIA

FHP, a successful and expanding HMO, has career opportunities available for BC/BE, residency-trained Family Practitioners and Specialists in: **Cardiology, Dermatology, ENT, Gastroenterology, Internal Medicine, OB/GYN, Orthopedics, Pediatrics, Psychiatry, Radiology, Rheumatology and Urology.** At FHP, you'll join an impressive roster of physicians carefully selected for their exceptional skills and talents. And you'll enjoy the financial rewards you deserve for being the best. Find out how FHP meets your personal and professional needs by calling (800) 446-2255, or (800) 336-2255 in California, or send CV to:

FHP Professional Staffing
9900 Talbert Ave, Department 45
Fountain Valley, CA 92708

An Equal Opportunity Employer.

KAISER PERMANENTE®

Good People. Good Medicine.

NORTHERN CALIFORNIA

Several positions available for Family Practice, Internal Medicine, and most subspecialties. We are a young aggressive group in a well known HMO organization with excellent benefits and a very reasonable call schedule. You will enjoy the patient population with ample time to enjoy the mountains and San Francisco which are nearby. If interested please call or send CV to Physician Recruitment, Administration, Kaiser Permanente Medical Group, Inc, 1305 Tommydon St, Stockton, CA 95210; (209) 476-3300.

SITUATION WANTED

RADIOLOGIST. BC for locum/part-time or full-time. (209) 931-4357: evenings, weekends, some days.

CHIEF MEDICAL RESIDENT AT MAJOR TEACHING HOSPITAL seeks Cardiology fellowship beginning 1988. Excellent recommendations. Reply to Number 92, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

INTERNIST/NEPHROLOGIST, BC, available April 1988. Willing to associate with established Internist group or establish a new Nephrology unit. Stand-alone or hospital associated dialysis in California. Contact A.A., PO Box 30726 TA, Los Angeles, CA 90030; (213) 734-6727, (213) 677-6396 message.

PRACTICES AVAILABLE

SOUTH SACRAMENTO AREA FAMILY PRACTICE. Collections of $111K in 1986. 95% insured patients. Full price: $50K. Seller financing available. Call Western Practice Sales (916) 673-1302.

CHICO AREA FAMILY PRACTICE. Collections of $246K in 1986. 2,600 square foot office. 92% cash patients. Seller will assist in transition. Call Western Practice Sales (916) 673-1302.

INTERNAL MEDICINE practice for sale in San Leandro, California. Well-staffed and equipped; fee-for-service near hospital; flexible terms. Inquiries to Number 87, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

SAN FRANCISCO BAY AREA. Growing industrial practice, owner relocating. Yearly billings $1,120,000. Principals only. Reply to Number 89, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

INTERNAL MEDICINE practice and equipment for sale (lab, fluoroscopy x-rays, spirogram, treadmill, computers, etc.). Gross six digits. Riverside, California. (714) 824-0364 after 8 PM.

BUY AN ARIZONA PRACTICE. We're the medical practice specialist of Arizona. FREE registration. Contact T. Ross, MD, Practice Opportunities, Realty Executives, 6520 N. Scottsdale Rd, M-110, Scottsdale, AZ 85253; (602) 991-4273.

OFFICE SPACE

GLENDALE, ARIZONA. Medical office space available. 705 square feet at the Thunderbird Medical Plaza I, 5422 W. Thunderbird Rd, Ste 19C, Glendale, AZ 85306. Call Sharad Bellapravalu, MD, (602) 938-1300.

SURGERY CENTER/MEDICAL OFFICE. Prime downtown San Francisco location, stunning decor professionally done, breathtaking views, prestigious waiting room, four exam/treatment rooms, two completely equipped operating rooms, recovery room, three business offices, kitchen, secretarial area, marble bathroom. Sale can be with or without equipment. 3,000 square feet total. Seven years remains on lease. Facility is three years old. This is a special prestigious facility being sold far below cost. Call Ken at (415) 398-2233.

MEDICAL PRACTICE OPPORTUNITIES

CALIFORNIA/NATIONWIDE. IM, Ped, Pulm, Cardio, Ortho, Surg, FP, Nutrition, Derm, Psych, OB/GYN, Oph, ENT, Urol, plus others. BRADSHAW ASSOCIATES, Practice Sales/Recruitment/Valuations, 21 Altamount Dr, Orinda, CA 94563; (415) 376-0762.

FINANCIAL SERVICES

FOR PHYSICIANS AND RESIDENTS. UNSECURED signature loans $5,000-$60,000, no points or fee, competitive rates—level payments, up to six years to repay. Deferred Principle Option. Confidential—rapid processing. For information and application call toll-free (800) 331-4952, MediVersal Dept. 114.

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SPONSORS OF COURSES—ABBREVIATIONS

AHA: American Heart Association, Utah Affiliate, 645 E 400 South, Salt Lake City 84102. (801) 322-5601.

BYUHS: Brigham Young University Health Services, McDonald Student Health Center, Brigham Young University, Provo 84602. (801) 378-2771.

CH: Castleview Hospital (formerly Carbon Hospital), RFD 2, Box 46, Price 84501. (801) 637-4800.

CWH: Cottonwood Hospital, 5770 S 300 East, Salt Lake City 84101. (801) 262-3461.

DMC: Dixie Medical Center, 544 S 400 East, St George 84770. (801) 673-9681.

HCH: Holy Cross Hospital, 1045 E First South, Salt Lake City 84102. (801) 350-4744.

ITS: Intermountain Thoracic Society, 1616 S 11th East, Salt Lake City 84105. (801) 484-4456.

LDSH: LDS Hospital, 8th Ave and "C" St, Salt Lake City 84143. (801) 321-1100.

LRH: Logan Regional Hospital, 1400 N 5th East, Logan 84321. (801) 752-2050.

MDH: McKay-Dee Hospital Center, 3939 Harrison Blvd, Ogden 84409. (801) 399-4141.

MVH: Mountain View Hospital, 1000 E Highway 6, Payson 84651. (801) 465-9201.

144: 144th Evacuation Hospital, PO Box 8000, Salt Lake City 84108. (801) 524-3924.

OSS: Ogden Surgical Society, PO Box 9311, Ogden 84409.

PCMC: Primary Children's Medical Center, 320 12th Ave, Salt Lake City 84103. (801) 363-1221.

PVH: Pioneer Valley Hospital, 3460 S 4155 West, West Valley City 84120. (801) 968-9061.

SMH: St Mark's Hospital, 1200 E 3900 South, Salt Lake City 84117. (801) 268-7111.

UOS: Utah Ophthalmological Society, 540 E 500 South, Salt Lake City 84102. (801) 355-7477.

USH: Utah State Hospital, PO Box 270, Provo 84603-0270. (801) 373-4400.

UUMC: University of Utah Medical Center, 50 N Medical Dr, Salt Lake City 84132. (801) 581-2258.

UVRMC: Utah Valley Regional Medical Center, 1034 N Fifth West, Provo 84604. (801) 373-7850.

VAMC: Veterans Administration Medical Center, 500 Foothill Dr, Salt Lake City 84148. (801) 582-1565.

VVMC: Valley View Medical Center, 595 S 75 East, Cedar City 84720. (801) 586-6587.

WASHINGTON

This listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. To list Category 1 programs here please send information at least two months in advance to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 900, Seattle, WA 98121; or phone (206) 441-WSMA.

Brochures and registration forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

COURSE SPONSORS AND CONTACT INFORMATION

CME HARBORVIEW—Contact: Gayle Splater, Cytology Continuing Education, Dept. of Pathology, Harborview Medical Center, 325 Ninth Avenue, Seattle, WA 98104. (206) 223-5953.

CME PIERCE COUNTY—Contact: Mrs Maxine Bailey, Executive Director, College of Medical Education, 705 South Ninth, No. 203, Tacoma, WA 98405. (206) 627-7137.

U/W (UNIVERSITY OF WASHINGTON)—Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

WSMA—Washington State Medical Association, Continuing Medical Education, 2033 Sixth Ave, Suite 900, Seattle, WA 98121. (206) 441-9762.

VMMC (VIRGINIA MASON MEDICAL CENTER)—Contact: Linda Orgel, Division of Continuing Medical Education, Virginia Mason Medical Center, PO Box 900, Seattle, WA 98111. (206) 223-6898.

March 15—**Washington State Academy of Ophthalmology Monthly Meeting.** TBA. Tues. Contact: Patti Smith, (206) 441-9762.

March 18-19—**NW Regional Rural Health Conference. Rural Health: Strategies and Solutions.** Spokane. Fri-Sat. Contact: ICNE, (509) 325-6146.

March 19-23—**11th Annual Physical Medicine and Rehabilitation Review.** Seattle. Sat-Wed. Contact: Maria Lilja, (206) 543-1050.

March 19-23—**Death Investigation.** Seattle. Sat-Wed. Contact: Maria Lilja, (206) 543-1050.

March 19-26—**Advances in Drug Therapy.** Seattle. One week. Contact: U/W, (206) 543-1050.

March 23-25—**Spirometry Training for Worker Screening.** Seattle. Wed-Fri. Contact: U/W, (206) 543-1069.

March 24-25—**Current Issues in Nutrition.** Seattle. Thurs-Fri. Contact: U/W, (206) 543-1050.

March 25—**Update in Contrast Media: An Evening of Uroradiology.** Seattle. Fri. Contact: VMMC.

April 8-9—**Ethics in Clinical Medicine.** Seattle. Wed-Thurs. Contact: U/W, Maria Lilja, (206) 543-1050.

April 16-20—**American Radium Society—Seventieth Annual Meeting.** Seattle. Sat-Wed. Contact: Ms Suzanne Bohn, ARS, Philadelphia, PA. (215) 574-3179.

April 18-28—**Review of Physical Medicine and Rehabilitation.** Seattle. Sat-Sat-Tues. Contact: U/W, Maria Lilja, (206) 543-1050.

April 19—**Washington State Academy of Ophthalmology Monthly Meeting.** TBA. Tues. Contact: Pattie Smith, (206) 441-9762.

April 19-23—**Death Investigation.** Seattle. Sun-Thurs. Contact: U/W, Maria Lilja, (206) 543-1050.

April 28-29—**Oncology.** Seattle. Tues-Wed. Contact: U/W, Maria Lilja, (206) 543-1050.

May 5-6—**Health Effects of Synthetic Fibers.** Seattle. Thurs-Fri. Contact: U/W, (206) 543-1069.

May 13—**Current Drug Topics—Pharmacology for the Practitioner.** Seattle. Fri. Contact: VMMC.

May 19-20—**Travel and Medicine.** Seattle. Thurs-Fri. Contact: Maria Lilja, (206) 543-1050.

May 19-21—**Emergency Medicine Update.** Seattle. Thurs-Sat. Contact: VMMC.

June 3—**Topics in General Internal Medicine.** Seattle. Fri. Contact: VMMC.

June 9-11—**Obstetric Ultrasound.** Seattle. Thurs-Sat. Contact: Robin Murray, (202) 863-2543.

June 20-24—**Pathology of Lung Cancer.** Seattle. Mon-Fri. Contact: VMMC.

July 29-31—**Seafair Anesthesia X.** Seattle. Fri-Sun. Contact: VMMC.

August 5—**Otology Update.** Seattle. Fri. Contact: VMMC.

August 29—**NW Regional Perinatal Conference: Current Issues in OB/GYN, Neonatology and Pediatrics.** Coeur d'Alene, Idaho. Thurs. Contact: (509) 624-3182.

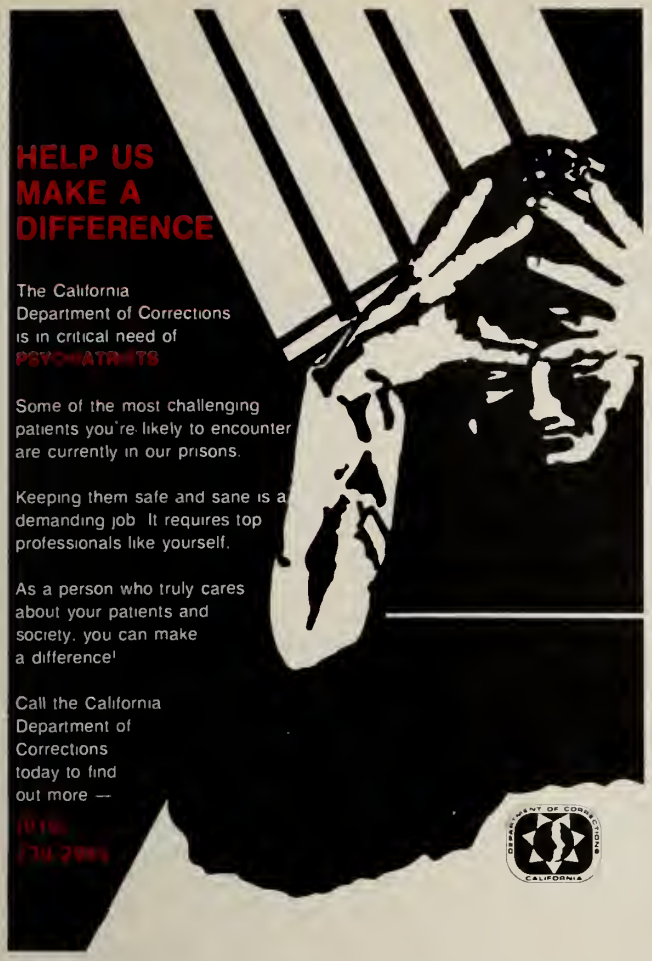
September 17-24—**Effective Management of Common Sports Injuries.** San Juan Islands. Sat-Sat. Contact: Kathy Rairigh, EPIC Expeditions, (208) 788-4995.

September 22-24—**Orthopedic Biomechanics.** Seattle. Thurs-Sat. Contact: VMMC.

WYOMING

June 23-26—**Wyoming Medical Society Annual Meeting.** Jackson Lake Lodge, Moran. Thurs-Sun. Contact: WMS, PO Drawer 4009, Cheyenne 82003-4009. (307) 635-2424.

July 17-22—**6th Annual Update in Clinical Microbiology and Immunology.** University of Utah Medical Center at Jackson Hole. Sun-Fri. 25 hrs. Contact: UUMC, 50 N. Medical Dr, Salt Lake City, UT 84132. (801) 581-2258. ◆



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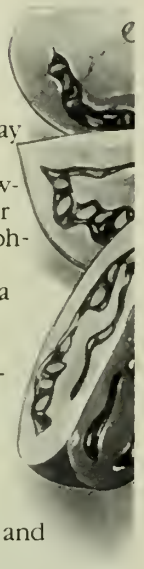
A defense against cancer can be cooked up in your kitchen.



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Foods that may help reduce the risk of gastrointestinal and respiratory tract cancer are cabbage, broccoli, brussels sprouts, kohlrabi, cauliflower.

Fruits, vegetables and whole-grain cereals such as oatmeal, bran and wheat may help lower the risk of colorectal cancer.

Foods high in fats, salt- or nitrite-cured foods such as ham, and fish and types of sausages smoked by traditional methods should be eaten in moderation.

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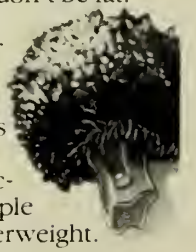

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California Medical Association—PO Box 7690, San Francisco 94120-7690. (415) 541-0900. Annual Meeting: March 4-9, 1988, Bally's Grand Hotel, Reno.

Colorado Medical Society—PO Box 17550, Denver 80217-0550. (303) 779-5455. Annual Meeting: September 15-17, 1988, Marriott City Center, Denver.

Hawaii Medical Association—320 Ward Ave, Suite 200, Honolulu 96814. (808) 536-7702. Annual Meeting: October 10-12, 1987, Kauai Surf, Kauai.

Idaho Medical Association—305 W Jefferson, PO Box 2668, Boise 83701. (208) 344-7888. Annual Meeting: July 21-23, 1988, Sun Valley.

Montana Medical Association—2012 11th Ave, Suite 12, Helena 59601. (406) 443-4000. Annual Meeting: September 29-October 1, 1988, Heritage Inn, Great Falls.

Nevada State Medical Association—3660 Baker Lane, Reno 89502. (702) 825-6788. Annual Meeting: April 21-24, 1988, Laughlin.

New Mexico Medical Society—303 San Mateo NE, Suite 204, Albuquerque 87108. (505) 266-7868. Annual Meeting: May 5-7, 1988, Hilton Inn, Albuquerque.

Oregon Medical Association—5210 SW Corbett Ave, Portland 97201. (503) 226-1555. Annual Meeting: (House of Delegates only): November 6-8, 1987, Portland.

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Rocephin® ROCHE® IV·IM

ceftriaxone sodium/Roche

Before prescribing, please consuft complete product information, a summary of which follows:

INOICATIONS ANO USAGE: Rocephin is indicated for the treatment of the following infections when caused by susceptible organisms

LOWER RESPIRATORY TRACT INFECTIONS caused by *Strep pneumoniae, Streptococcus* species (excluding enterococci), *Staph aureus, H influenzae, H parainfluenzae, Klebsiella* species (including *K pneumoniae*), *E coli, E aerogenes, Proteus mirabilis* and *Serratia marcescens*

SKIN AND SKIN STRUCTURE INFECTIONS caused by *Staph aureus, Staph epidermidis, Streptococcus* species (excluding enterococci), *E cloacae, Klebsiella* species (including *K pneumoniae*), *Proteus mirabilis* and *Pseudomonas aeruginosa*

URINARY TRACT INFECTIONS (complicated and uncomplicated) caused by *E coli, Proteus mirabilis, Proteus vulgaris, M morganii* and *Klebsiella* species (including *K pneumoniae*)

UNCOMPLICATED GONORRHEA (cervical/urethral and rectal) caused by *Neisseria gonorrhoeae*, including both penicillinase and nonpenicillinase producing strains

PELVIC INFLAMMATORY DISEASE caused by *N gonorrhoeae*

BACTERIAL SEPTICEMIA caused by *Staph aureus, Strep pneumoniae, E coli, H influenzae* and *K pneumoniae*

BONE AND JOINT INFECTIONS caused by *Staph aureus, Strep pneumoniae, Streptococcus* species (excluding enterococci), *E coli, P mirabilis, K pneumoniae* and *Enterobacter* species

INTRA-ABDOMINAL INFECTIONS caused by *E coli* and *K pneumoniae*

MENINGITIS caused by *H influenzae, N meningitidis* and *Strep pneumoniae* Ceftriaxone has also been used successfully in a limited number of cases of meningitis and shunt infections caused by *Staph epidermidis* and *E coli*

SURGICAL PROPHYLAXIS Preoperative administration of a single 1 gm dose may reduce incidence of postoperative infections in patients undergoing surgical procedures classified as contaminated or potentially contaminated (e g , vaginal or abdominal hysterectomy) and in those for whom infection at the operative site presents serious risk (e g , during coronary artery bypass surgery)

Although ceftriaxone has been shown to have been as effective as cefazolin in the prevention of infection following coronary artery bypass surgery no placebo-controlled trials have been conducted to evaluate any cephalosporin antibiotic in the prevention of infection following coronary artery bypass surgery When administered before indicated surgical procedures, a single 1 gm dose provides protection from most infections due to susceptible organisms for duration of procedure

SUSCEPTIBILITY TESTING Before instituting treatment with Rocephin appropriate specimens should be obtained for isolation of the causative organism and for determination of its susceptibility to the drug Therapy may be instituted prior to obtaining results of susceptibility testing

CONTRAINOICATIONS: Rocephin is contraindicated in patients with known allergy to the cephalosporin class of antibiotics

WARNINGS: BEFORE THERAPY WITH ROCEPHIN IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE TO DETERMINE WHETHER THE PATIENT HAS HAD PREVIOUS HYPERSENSITIVITY REACTIONS TO CEPHALOSPORINS PENICILLINS OR OTHER DRUGS THIS PRODUCT SHOULD BE GIVEN CAUTIOUSLY TO PENICILLIN-SENSITIVE PATIENTS ANTIBIOTICS SHOULD BE ADMINISTERED WITH CAUTION TO ANY PATIENT WHO HAS DEMONSTRATED SOME FORM OF ALLERGY PARTICULARLY TO DRUGS SERIOUS ACUTE HYPERSENSITIVITY REACTIONS MAY REQUIRE THE USE OF SUBCUTANEOUS EPINEPHRINE AND OTHER EMERGENCY MEASURES

Pseudomembranous colitis has been reported with the use of cephalosporins (and other broad-spectrum antibiotics), therefore, it is important to consider its diagnosis in patients who develop diarrhea in association with antibiotic use

Treatment with broad-spectrum antibiotics alters the normal flora of the colon and may permit overgrowth of clostridia Studies indicate a toxin produced by *Clostridium difficile* is one primary cause of antibiotic-associated colitis Cholestyramine and colestipol resins have been shown to bind to the toxin *in vitro*

Mild cases of colitis respond to drug discontinuance alone Moderate to severe cases should be managed with fluid, electrolyte and protein supplementation as indicated

When the colitis is not relieved by drug discontinuance or when it is severe, oral vancomycin is the treatment of choice for antibiotic-associated pseudomembranous colitis produced by *C difficile* Other causes of colitis should also be considered

Rarely, shadows suggesting sludge have been detected by sonograms of the gallbladder in asymptomatic and symptomatic patients This appears to be reversible on discontinuation of therapy In a few symptomatic patients receiving higher than usual doses, who underwent surgery, sludge containing traces of ceftriaxone was recovered from surgical specimens Discontinue therapy in patients who develop signs or symptoms suggestive of gallbladder disease, consider conservative management

PRECAUTIONS: *GENERAL* Although transient elevations of BUN and serum creatinine have been observed, at the recommended dosages the nephrotoxic potential of Rocephin is similar to that of other cephalosporins

Ceftriaxone is excreted via both biliary and renal excretion (see Clinical Pharmacology) Therefore, patients with renal failure normally require no adjustment in dosage when usual doses of Rocephin are administered, but concentrations of drug in the serum should be monitored periodically If evidence of accumulation exists dosage should be decreased accordingly

Dosage adjustments should not be necessary in patients with hepatic dysfunction, however, in patients with both hepatic dysfunction and significant renal disease Rocephin dosage should not exceed 2 gm daily without close monitoring of serum concentrations

Alterations in prothrombin times have occurred rarely in patients treated with Rocephin Patients with impaired vitamin K synthesis or low vitamin K stores (e g chronic hepatic disease and malnutrition) may require monitoring of prothrombin time during Rocephin treatment Vitamin K administration (10 mg weekly) may be necessary if the prothrombin time is prolonged before or during therapy

Prolonged use of Rocephin may result in overgrowth of nonsusceptible organisms Careful observation of the patient is essential If superinfection occurs during therapy, appropriate measures should be taken

Rocephin should be prescribed with caution in individuals with a history of gastrointestinal disease, especially colitis

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY Carcinogenesis Considering the maximum duration of treatment and the class of the compound carcinogenicity studies with ceftriaxone in animals have not been performed The maximum

ROCEPHIN* (ceftriaxone sodium/Roche)

duration of animal toxicity studies was six months

Mutagenesis Genetic toxicology tests included the Ames test a micronucleus test and a test for chromosomal aberrations in human lymphocytes cultured *in vitro* with ceftriaxone Ceftriaxone showed no potential for mutagenic activity in these studies

Impairment of Fertility Ceftriaxone produced no impairment of fertility when given intravenously to rats at daily doses up to 586 mg/kg/day approximately 20 times the recommended clinical dose of 2 gm/day

PREGNANCY Teratogenic Effects Pregnancy Category B Reproductive studies have been performed in mice and rats at doses up to 20 times the usual human dose and have no evidence of embryotoxicity fetotoxicity or teratogenicity In primates no embryotoxicity or teratogenicity was demonstrated at a dose approximately three times the human dose

There are, however, no adequate and well-controlled studies in pregnant women Because animal reproductive studies are not always predictive of human response this drug should be used during pregnancy only if clearly needed

Nonteratogenic Effects In rats in the Segment I (fertility and general reproduction) and Segment III (perinatal and postnatal) studies with intravenously administered ceftriaxone no adverse effects were noted on various reproductive parameters during gestation and lactation, including postnatal growth functional behavior and reproductive ability of the offspring at doses of 586 mg/kg/day or less

NURSING MOTHERS Low concentrations of ceftriaxone are excreted in human milk Caution should be exercised when Rocephin is administered to a nursing woman

PEDIATRIC USE Safety and effectiveness of Rocephin in neonates, infants and children have been established for the dosages described in the Dosage and Administration section *In vitro* studies have shown ceftriaxone like some other cephalosporins can displace bilirubin from serum albumin Exercise caution before administration to hyperbilirubinemic neonates, especially prematures

AOVERSE REACTIONS: Rocephin is generally well tolerated In clinical trials, the following adverse reactions, which were considered to be related to Rocephin therapy or of uncertain etiology were observed

LOCAL REACTIONS—pain, induration or tenderness at the site of injection (1%) Less frequently reported (less than 1%) was phlebitis after I V administration

HYPERSENSITIVITY—rash (1 7%) Less frequently reported (less than 1%) were pruritus, fever or chills

HEMATOLOGIC—eosinophilia (6%), thrombocytosis (5 1%) and leukopenia (2 1%) Less frequently reported (less than 1%) were anemia neutropenia lymphopenia thrombocytopenia and prolongation of the prothrombin time

GASTROINTESTINAL—diarrhea (2 7%) Less frequently reported (less than 1%) were nausea or vomiting and dysgeusia

HEPATIC—elevations of SGOT (3 1%) or SGPT (3 3%) Less frequently reported (less than 1%) were elevations of alkaline phosphatase and bilirubin

RENAL elevations of the BUN (1 2%) Less frequently reported (less than 1%) were elevations of creatinine and the presence of casts in the urine

CENTRAL NERVOUS SYSTEM headache or dizziness were reported occasionally (less than 1%)

GENITOURINARY—moniliasis or vaginitis were reported occasionally (less than 1%)

MISCELLANEOUS—diaphoresis and flushing were reported occasionally (less than 1%)

Other rarely observed adverse reactions (less than 0 1%) include leukocytosis, lymphocytosis, monocytosis, basophilia a decrease in the prothrombin time, jaundice, gallbladder sludge glycosuria hematuria anaphylaxis, bronchospasm, serum sickness abdominal pain colitis, flatulence, dyspepsia palpitations and epistaxis

DOSAGE ANO ADMINISTRATION: Rocephin may be administered intravenously or intramuscularly The usual adult daily dose is 1 to 2 gm given once a day (or in equally divided doses twice a day) depending on the type and severity of the infection The total daily dose should not exceed 4 grams

For the treatment of serious miscellaneous infections in children, other than meningitis the recommended total daily dose is 50 to 75 mg/kg (not to exceed 2 grams) given in divided doses every 12 hours

Generally, Rocephin therapy should be continued for at least two days after the signs and symptoms of infection have disappeared The usual duration is 4 to 14 days, in complicated infections longer therapy may be required

In the treatment of meningitis, a daily dose of 100 mg/kg (not to exceed 4 grams), given in divided doses every 12 hours should be administered with or without a loading dose of 75 mg/kg

For the treatment of uncomplicated gonococcal infections, a single intramuscular dose of 250 mg is recommended

For preoperative use (surgical prophylaxis), a single dose of 1 gm administered 1/2 to 2 hours before surgery is recommended

When treating infections caused by *Streptococcus pyogenes*, therapy should be continued for at least ten days

No dosage adjustment is necessary for patients with impairment of renal or hepatic function, however blood levels should be monitored in patients with severe renal impairment (e g dialysis patients) and in patients with both renal and hepatic dysfunctions

HOW SUPPLIEO: Rocephin (ceftriaxone sodium/Roche) is supplied as a sterile crystalline powder in glass vials and piggyback bottles The following packages are available

Vials containing 250 mg 500 mg 1 gm or 2 gm equivalent of ceftriaxone, piggyback bottles containing 1 gm or 2 gm equivalent of ceftriaxone, bulk pharmacy containers containing 10 gm equivalent of ceftriaxone (NOT FOR DIRECT ADMINISTRATION)

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1 gm equivalent of ceftriaxone iso-osmotic with approximately 1 9 gm dextrose hydrous, USP added

2 gm equivalent of ceftriaxone iso-osmotic with approximately 1 2 gm dextrose hydrous USP added

NOTE Rocephin in the frozen state should not be stored above -20°C

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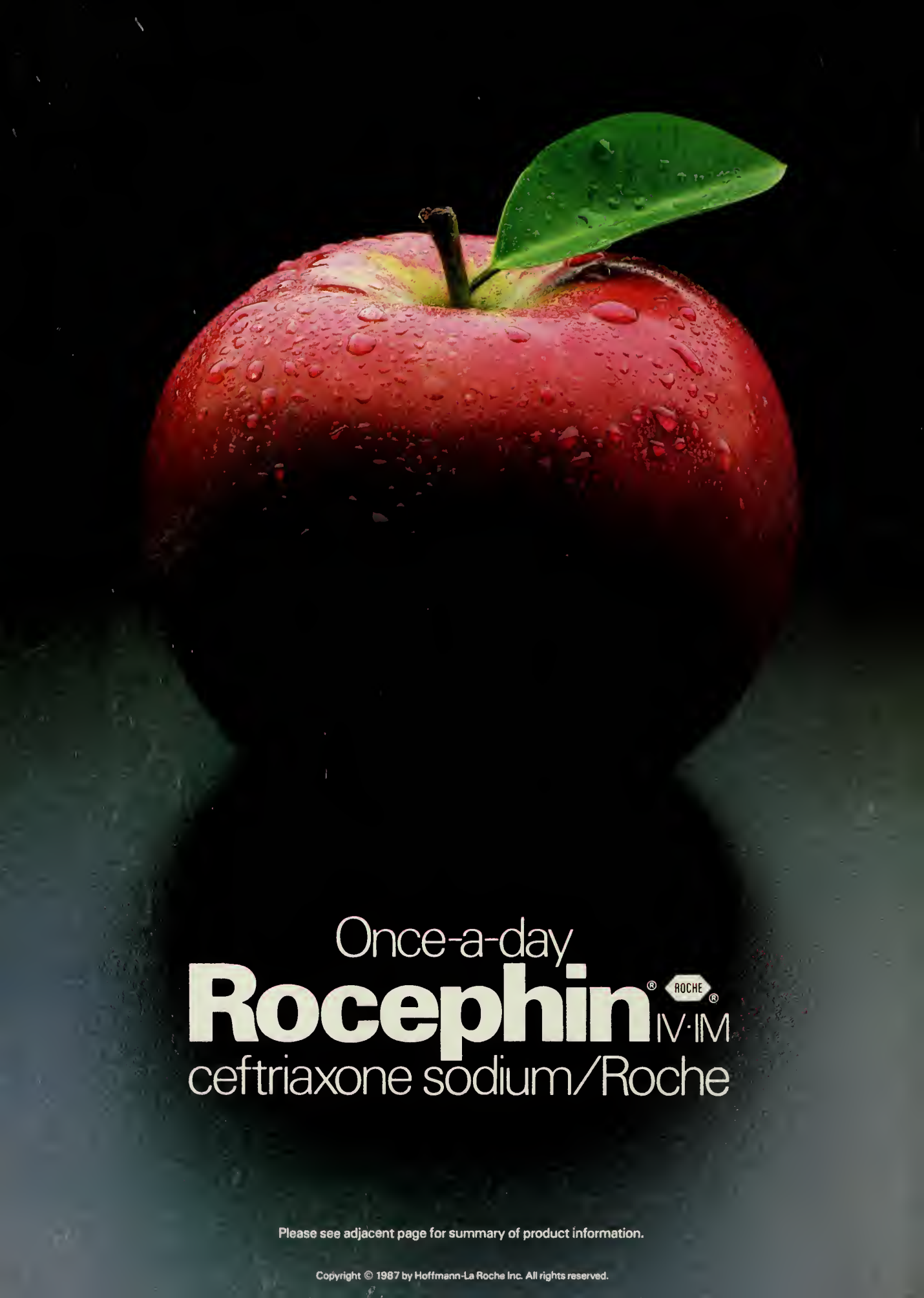
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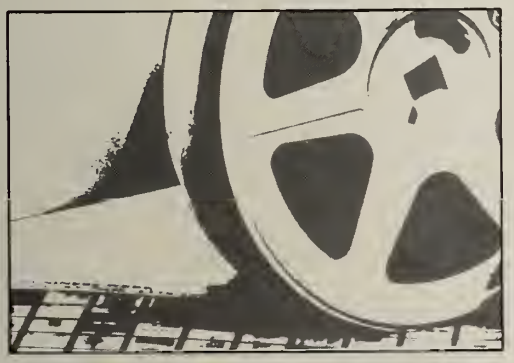

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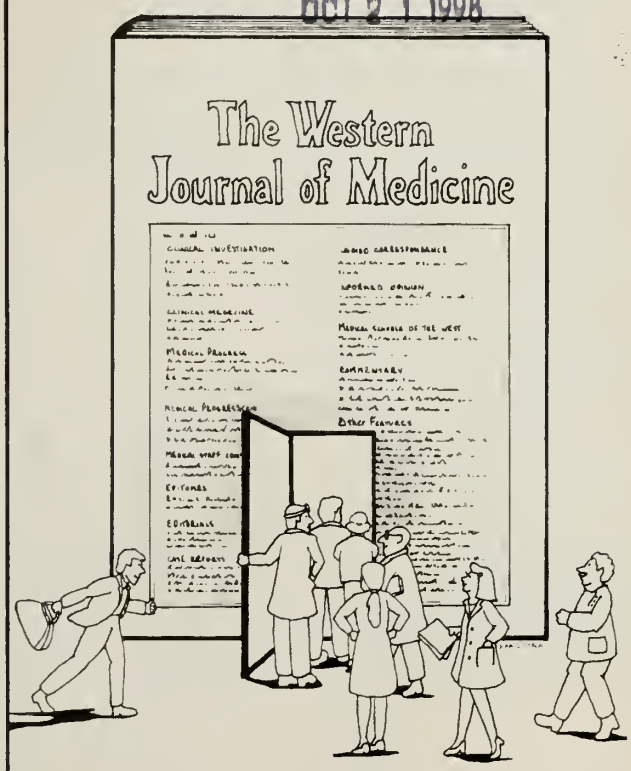

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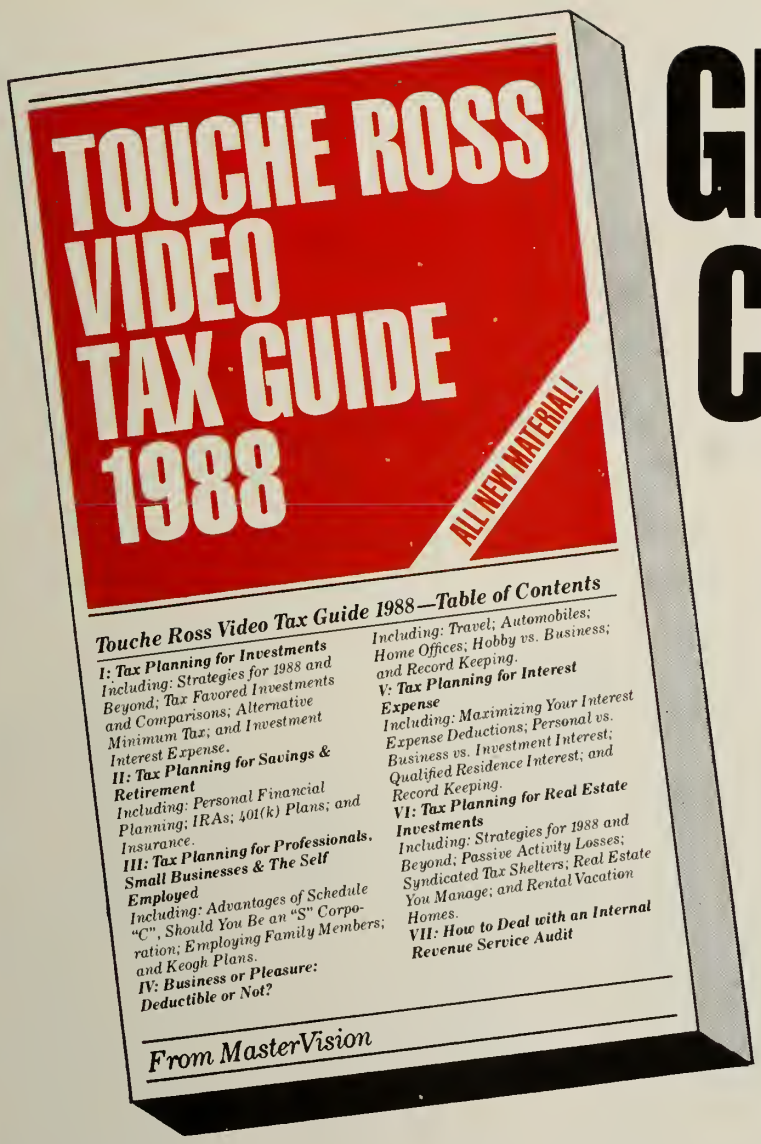

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1. Croog SH, Levine S, Testa MA, et al: The effects of antihypertensive therapy on the quality of life. N Engl J Med 314(26):1657-1664, 1986.
2. Data on file, University of Connecticut.

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WARNINGS: Neutropenia/Agranulocytosis—Neutropenia ($<1000/mm^3$) with myeloid hypoplasia has resulted from use of captopril. About half of the neutropenic patients developed systemic or oral cavity infections or other features of the syndrome of agranulocytosis. The risk of neutropenia is dependent on the clinical status of the patient:

In clinical trials in patients with hypertension who have normal renal function (serum creatinine less than 1.6 mg/dL and no collagen vascular disease), neutropenia has been seen in one patient out of over 8,600 exposed. In patients with some degree of renal failure (serum creatinine at least 1.6 mg/dL) but no collagen vascular disease, the risk in clinical trials was about 1 per 500. Doses were relatively high in these patients, particularly in view of their diminished renal function. In patients with collagen vascular diseases (e.g., systemic lupus erythematosus, scleroderma) and impaired renal function, neutropenia occurred in 3.7% of patients in clinical trials. While none of the over 750 patients in formal clinical trials of heart failure developed neutropenia, it has occurred during the subsequent clinical experience. Of reported cases, about half had serum creatinine $\geq$1.6 mg/dL and more than 75% received procainamide. In heart failure, it appears that the same risk factors for neutropenia are present.

Neutropenia has appeared usually within 3 months after starting therapy, associated with myeloid hypoplasia and frequently accompanied by erythroid hypoplasia and decreased numbers of megakaryocytes (e.g., hypoplastic bone marrow and pancytopenia); anemia and thrombocytopenia were sometimes seen. Neutrophils generally returned to normal in about 2 weeks after captopril was discontinued, and serious infections were limited to clinically complex patients. About 13% of the cases of neutropenia have ended fatally, but almost all fatalities were in patients with serious illness, having collagen vascular disease, renal failure, heart failure or immunosuppressant therapy, or a combination of these complicating factors. **Evaluation of the hypertensive or heart failure patient should always include assessment of renal function.** If captopril is used in patients with impaired renal function, white blood cell and differential counts should be evaluated prior to starting treatment and at approximately 2-week intervals for about 3 months, then periodically. In patients with collagen vascular disease or who are exposed to other drugs known to affect the white cells or immune response, particularly when there is impaired renal function, captopril should be used only after an assessment of benefit and risk, and then with caution. All patients treated with captopril should be told to report any signs of infection (e.g., sore throat, fever). If infection is suspected, perform white cell counts without delay. Since discontinuation of captopril and other drugs has generally led to prompt return of the white count to normal, upon confirmation of neutropenia (neutrophil count $<1000/mm^3$) withdraw captopril and closely follow the patient's course.

Proteinuria: Total urinary proteins $>$1 g per day were seen in about 0.7% of patients on captopril. About 90% of affected patients had evidence of prior renal disease or received high doses ($>$150 mg/day), or both. The nephrotic syndrome occurred in about one-fifth of proteinuric patients. In most cases, proteinuria subsided or cleared within 6 months whether or not captopril was continued. The BUN and creatinine were seldom altered in proteinuric patients. Since most cases of proteinuria occurred by the 8th month of therapy with captopril, patients with prior renal disease or those receiving captopril at doses $>$150 mg per day, should have urinary protein estimates (dip-stick on 1st morning urine) before therapy, and periodically thereafter.

Hypotension: Excessive hypotension was rarely seen in hypertensive patients but is a possibility in severely salt/volume-depleted persons such as those treated vigorously with diuretics (see PRECAUTIONS [Drug Interactions]). In heart failure, where the blood pressure was either normal or low, transient decreases in mean blood pressure $>$20% were recorded in about half of the patients. This transient hypotension may occur after any of the first several doses and is usually well tolerated, although rarely it has been associated with arrhythmia or conduction defects. A starting dose of 6.25 or 12.5 mg tid may minimize the hypotensive effect. Patients should be followed closely for the first 2 weeks of treatment and whenever the dose of captopril and/or diuretic is increased.

BECAUSE OF THE POTENTIAL FALL IN BLOOD PRESSURE IN THESE PATIENTS, THERAPY SHOULD BE STARTED UNDER VERY CLOSE MEDICAL SUPERVISION.

PRECAUTIONS: General: *Impaired Renal Function*—Hypertension—Some hypertensive patients with renal disease, particularly those with severe renal artery stenosis, have developed increases in BUN and serum creatinine. It may be necessary to reduce captopril dosage and/or discontinue diuretic. For some of these patients, normalization of blood pressure and maintenance of adequate renal perfusion may not be possible. Heart Failure—About 20% of patients develop stable elevations of BUN and serum creatinine $>$20% above normal or baseline upon long-term treatment. Less than 5% of patients, generally with severe preexisting renal disease, required discontinuation due to progressively increasing creatinine. See DOSAGE AND ADMINISTRATION, ADVERSE REACTIONS [Altered Laboratory Findings]. *Valvular Stenosis*—A theoretical concern, for risk of decreased coronary perfusion, has been noted regarding vasodilator treatment in patients with aortic stenosis due to decreased afterload reduction. *Surgery/Anesthesia*—If hypotension occurs during surgery or anesthesia, and is considered due to the effects of captopril, it is correctable by volume expansion.

Drug Interactions: *Hypotension—Patients on Diuretic Therapy*—Precipitous reduction of blood pressure may occasionally occur within the 1st hour after administration of the initial of captopril dose in patients on diuretics, especially those recently placed on diuretics, and those on severe dietary salt restriction or dialysis. This possibility can be minimized by either discontinuing the diuretic or increasing the salt intake about 1 week prior to initiation of captopril therapy or by initiating therapy with small doses (6.25 or 12.5 mg). Alternatively, provide medical supervision for at least 1 hour after the initial dose.

Agents Having Vasodilator Activity—In heart failure patients, vasodilators should be administered with caution.

Agents Causing Renin Release—Captopril's effect will be augmented by antihypertensive agents that cause renin release.

Agents Affecting Sympathetic Activity—The sympathetic nervous system may be especially important in supporting blood pressure in patients receiving captopril alone or with diuretics. Beta-adrenergic blocking drugs add some further antihypertensive effect to captopril, but the overall response is less than additive. Therefore, use agents affecting sympathetic activity (e.g., ganglionic blocking agents or adrenergic neuron blocking agents) with caution.

Agents Increasing Serum Potassium—Give potassium-sparing diuretics or potassium supplements only for documented hypokalemia, and then with caution, since they may lead to a significant increase of serum potassium. Use potassium-containing salt substitutes with caution.

Inhibitors of Endogenous Prostaglandin Synthesis—Indomethacin and other nonsteroidal anti-inflammatory agents may reduce the antihypertensive effect of captopril, especially in low renin hypertension.

Drug/Laboratory Test Interaction: Captopril may cause a false-positive urine test for acetone.

Carcinogenesis, Mutagenesis and Impairment of Fertility: Two-year studies with doses of 50 to 1350 mg/kg/day in mice and rats failed to show any evidence of carcinogenic potential. Studies in rats have revealed no impairment of fertility.

Pregnancy: Category C: There are no adequate and well-controlled studies in pregnant women. Embryocidal effects and craniofacial malformations were observed in rabbits. Therefore, captopril should be used during pregnancy, or for patients likely to become pregnant, only if the potential benefit outweighs the potential risk to the fetus. Captopril crosses the human placenta.

Nursing Mothers: Captopril is secreted in human milk. Exercise caution when administering captopril to a nursing woman, and, in general, nursing should be interrupted.

Pediatric Use: Safety and effectiveness in children have not been established although there is limited experience with use of captopril in children from 2 months to 15 years of age. Dosage, on a weight basis, was comparable to that used in adults. CAPOTEN (captopril) should be used in children only if other measures for controlling blood pressure have not been effective.

ADVERSE REACTIONS: Reported incidences are based on clinical trials involving approximately 7000 patients.

Renal—About 1 of 100 patients developed proteinuria (see WARNINGS). Renal insufficiency, renal failure, polyuria, oliguria, and urinary frequency in 1 to 2 of 1000 patients.

Hematologic—Neutropenia/agranulocytosis has occurred (see WARNINGS). Anemia, thrombocytopenia, and pancytopenia have been reported.

Dermatologic—Rash, (usually maculopapular, rarely urticarial), often with pruritus, and sometimes with fever and eosinophilia, in about 4 to 7 of 100 patients (depending on renal status and dose), usually during the 1st 4 weeks of therapy. Pruritus, without rash, in about 2 of 100 patients. A reversible associated pemphigoid-like lesion, and photosensitivity, have also been reported. Angioedema of the face, mucous membranes of the mouth, or of the extremities in about 1 of 1000 patients—reversible on discontinuance of captopril therapy. One case of laryngeal edema has been reported. Flushing or pallor in 2 to 5 of 1000 patients.

Cardiovascular—Hypotension may occur; see WARNINGS and PRECAUTIONS [Drug Interactions] for discussion of hypotension on initiation of captopril therapy. Tachycardia, chest pain, and palpitations each in about 1 of 100 patients. Angina pectoris, myocardial infarction, Raynaud's syndrome, and congestive heart failure each in 2 to 3 of 1000 patients.

Dysgeusia—Approximately 2 to 4 (depending on renal status and dose) of 100 patients developed a diminution or loss of taste perception; taste impairment is reversible and usually self-limited even with continued drug use (2 to 3 months). Gastric irritation, abdominal pain, nausea, vomiting, diarrhea, anorexia, constipation, aphthous ulcers, peptic ulcer, dizziness, headache, malaise, fatigue, insomnia, dry mouth, dyspnea, cough, alopecia, paresthesias reported in about 0.5 to 2% of patients but did not appear at increased frequency compared to placebo or other treatments used in controlled trials.

Altered Laboratory Findings: Elevations of liver enzymes in a few patients although no causal relationship has been established. Rarely cholestatic jaundice, and hepatocellular injury with or without secondary cholestasis, have been reported. A transient elevation of BUN and serum creatinine may occur, especially in volume-depleted or renovascular hypertension patients. In instances of rapid reduction of longstanding or severely elevated blood pressure, the glomerular filtration rate may decrease transiently, also resulting in transient rises in serum creatinine and BUN. Small increases in serum potassium concentration frequently occur, especially in patients with renal impairment (see PRECAUTIONS).

OVERDOSAGE: Primary concern is correction of hypotension. Volume expansion with an I.V. infusion of normal saline is the treatment of choice for restoration of blood pressure. Captopril may be removed from the general circulation by hemodialysis.

DOSAGE AND ADMINISTRATION: CAPOTEN (captopril) should be taken one hour before meals. In hypertension, CAPOTEN may be dosed bid or tid. Dosage must be individualized; see DOSAGE AND ADMINISTRATION section of package insert for detailed information regarding dosage in hypertension and in heart failure. Because CAPOTEN (captopril) is excreted primarily by the kidneys, dosage adjustments are recommended for patients with impaired renal function.

Consult package insert before prescribing CAPOTEN (captopril).

HOW SUPPLIED: Available in tablets of 12.5, 25, 50, and 100 mg in bottles of 100 (25 mg and 50 mg also available in bottles of 1000), and in UNIMATIC® unit-dose packs of 100 tablets. (J3-658J)

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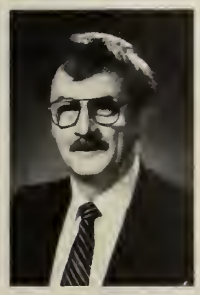

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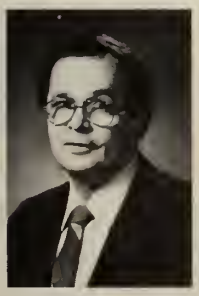

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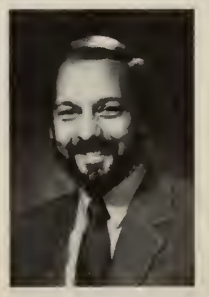

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60 mg GREATER DOSAGE FLEXIBILITY 90 mg/120 mg

*CARDIZEM® (diltiazem HCl) is indicated in the treatment of angina pectoris due to coronary artery spasm and in the management of chronic stable angina (classic effort-associated angina) in patients who cannot tolerate therapy with beta-blockers and/or nitrates or who remain symptomatic despite adequate doses of these agents.

†See Warnings and Precautions.

Please see brief summary of prescribing information on the next page.

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CARDIZEM® ANTIANGINAL PROTECTION PLUS SAFETY

diltiazem HCl/Marion

Usual maintenance dosage range: 180-360 mg/day

BRIEF SUMMARY
Professional Use Information
CARDIZEM®
(diltiazem HCl)
30 mg, 60 mg, 90 mg, and 120 mg Tablets

CONTRAINDICATIONS

CARDIZEM is contraindicated in (1) patients with sick sinus syndrome except in the presence of a functioning ventricular pacemaker, (2) patients with second- or third-degree AV block except in the presence of a functioning ventricular pacemaker, (3) patients with hypotension (less than 90 mm Hg systolic), and (4) patients who have demonstrated hypersensitivity to the drug.

WARNINGS

1. **Cardiac Conduction.** CARDIZEM prolongs AV node refractory periods without significantly prolonging sinus node recovery time, except in patients with sick sinus syndrome. This effect may rarely result in abnormally slow heart rates (particularly in patients with sick sinus syndrome) or second- or third-degree AV block (six of 1,243 patients for 0.48%). Concomitant use of diltiazem with beta-blockers or digitalis may result in additive effects on cardiac conduction. A patient with Prinzmetal's angina developed periods of asystole (2 to 5 seconds) after a single dose of 60 mg of diltiazem.
2. **Congestive Heart Failure.** Although diltiazem has a negative inotropic effect in isolated animal tissue preparations, hemodynamic studies in humans with normal ventricular function have not shown a reduction in cardiac index nor consistent negative effects on contractility (dp/dt). Experience with the use of CARDIZEM alone or in combination with beta-blockers in patients with impaired ventricular function is very limited. Caution should be exercised when using the drug in such patients.
3. **Hypotension.** Decreases in blood pressure associated with CARDIZEM therapy may occasionally result in symptomatic hypotension.
4. **Acute Hepatic Injury.** In rare instances, significant elevations in enzymes such as alkaline phosphatase, LDH, SGDT, SGPT, and other phenomena consistent with acute hepatic injury have been noted. These reactions have been reversible upon discontinuation of drug therapy. The relationship to CARDIZEM is uncertain in most cases, but probable in some. (See PRECAUTIONS.)

PRECAUTIONS

General. CARDIZEM (diltiazem hydrochloride) is extensively metabolized by the liver and excreted by the kidneys and in bile. As with any drug given over prolonged periods, laboratory parameters should be monitored at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function. In subacute and chronic dog and rat studies designed to produce toxicity, high doses of diltiazem were associated with hepatic damage. In special subacute hepatic studies, oral doses of 125 mg/kg and higher in rats were associated with histological changes in the liver which were reversible when the drug was discontinued. In dogs, doses of 20 mg/kg were also associated with hepatic changes; however, these changes were reversible with continued dosing.

Dermatological events (see ADVERSE REACTIONS section) may be transient and may disappear despite continued use of CARDIZEM. However, skin eruptions progressing to erythema multiforme and/or exfoliative dermatitis have also been infrequently reported. Should a dermatologic reaction persist, the drug should be discontinued.

Drug Interaction. Due to the potential for additive effects, caution and careful titration are warranted in patients receiving CARDIZEM concomitantly with any agents known to affect cardiac contractility and/or conduction. (See WARNINGS.)

Pharmacologic studies indicate that there may be additive effects in prolonging AV conduction when using beta-blockers or digitalis concomitantly with CARDIZEM. (See WARNINGS.)

As with all drugs, care should be exercised when treating patients with multiple medications. CARDIZEM undergoes biotransformation by cytochrome P-450 mixed function oxidase. Coadministration of CARDIZEM with other agents which follow the same route of biotransformation may result in the competitive inhibition of metabolism. Dosages of similarly metabolized drugs, particularly those of low therapeutic ratio or in patients with renal and/or hepatic impairment, may require adjustment when starting or stopping concomitantly administered CARDIZEM to maintain optimum therapeutic blood levels.

Beta-blockers: Controlled and uncontrolled domestic studies suggest that concomitant use of CARDIZEM and beta-blockers or digitalis is usually well tolerated. Available data are not sufficient, however, to predict the effects of concomitant treatment, particularly in patients with left ventricular dysfunction or cardiac conduction abnormalities.

Administration of CARDIZEM (diltiazem hydrochloride) concomitantly with propranolol in five normal volunteers resulted in increased propranolol levels in all subjects and bioavailability of propranolol was increased approximately 50%. If combination therapy is initiated or withdrawn in conjunction with propranolol, an adjustment in the propranolol dose may be warranted. (See WARNINGS.)

Cimetidine: A study in six healthy volunteers has shown a significant increase in peak diltiazem plasma levels (58%) and area-under-the-curve (53%) after a one-week course of cimetidine at 1,200 mg per day and diltiazem 60 mg per day. Ranitidine produced smaller, nonsignificant increases. The effect may be mediated by cimetidine's known inhibition of hepatic cytochrome P-450, the enzyme system probably responsible for the first-pass metabolism of diltiazem. Patients currently receiving diltiazem therapy should be carefully monitored for a change in pharmacological effect when initiating and discontinuing therapy with cimetidine. An adjustment in the diltiazem dose may be warranted.

Digitalis: Administration of CARDIZEM with digoxin in 24 healthy male subjects increased plasma digoxin concentrations approximately 20%. Another investigator found no increase in digoxin levels in 12 patients with coronary artery disease. Since there have been conflicting results regarding the effect of digoxin levels, it is recommended that digoxin levels be monitored when initiating, adjusting, and discontinuing CARDIZEM therapy to avoid possible over- or under-digitalization. (See WARNINGS.)

Carcinogenesis, Mutagenesis, Impairment of Fertility. A 24-month study in rats and a 21-month study in mice showed no evidence of carcinogenicity. There was also no mutagenic response in in vitro bacterial tests. No intrinsic effect on fertility was observed in rats.

Pregnancy. Category C. Reproduction studies have been conducted in mice, rats, and rabbits. Administration of doses ranging from five to ten times greater (on a mg/kg basis) than the daily recommended therapeutic dose has resulted in embryo and fetal lethality. These doses, in some studies, have been reported to cause skeletal abnormalities. In the perinatal/ postnatal studies, there was some reduction in early individual pup weights and survival rates. There was an increased incidence of stillbirths at doses of 20 times the human dose or greater.

There are no well-controlled studies in pregnant women; therefore, use CARDIZEM in pregnant women only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers. Diltiazem is excreted in human milk. One report suggests that concentrations in breast milk may approximate serum levels. If use of CARDIZEM is deemed essential, an alternative method of infant feeding should be instituted.

Pediatric Use. Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Serious adverse reactions have been rare in studies carried out to date, but it should be recognized that patients with impaired ventricular function and cardiac conduction abnormalities have usually been excluded.

In domestic placebo-controlled trials, the incidence of adverse reactions reported during CARDIZEM therapy was not greater than that reported during placebo therapy.

The following represent occurrences observed in clinical studies which can be at least reasonably associated with the pharmacology of calcium influx inhibition. In many cases, the relationship to CARDIZEM has not been established. The most common occurrences as well as their frequency of presentation are: edema (2.4%), headache (2.1%), nausea (1.9%), dizziness (1.5%), rash (1.3%), asthenia (1.2%). In addition, the following events were reported infrequently (less than 1%):

Cardiovascular:	Angina, arrhythmia, AV block (first degree), AV block (second or third degree—see conduction warning), bradycardia, congestive heart failure, flushing, hypotension, palpitations, syncope.
Nervous System:	Amnesia, depression, gait abnormality, hallucinations, insomnia, nervousness, paresthesia, personality change, somnolence, tinnitus, tremor.
Gastrointestinal:	Anorexia, constipation, diarrhea, dysgeusia, dyspepsia, mild elevations of alkaline phosphatase, SGDT, SGPT, and LDH (see hepatic warnings), vomiting, weight increase.
Dermatologic:	Petechiae, pruritus, photosensitivity, urticaria.
Other:	Amblyopia, CPK elevation, dyspnea, epistaxis, eye irritation, hyperglycemia, nasal congestion, nocturia, osteoarticular pain, polyuria, sexual difficulties.

The following postmarketing events have been reported infrequently in patients receiving CARDIZEM: alopecia, gingival hyperplasia, erythema multiforme, and leukopenia. However, a definitive cause and effect between these events and CARDIZEM therapy is yet to be established. Issued 6/87

See complete Professional Use Information before prescribing

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Please see next page for brief summary of prescribing information, including warnings, precautions, and adverse reactions.

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(clonidine)/TRANSDERMAL THERAPEUTIC SYSTEM

Programmed delivery *in vivo* of 0.1, 0.2 or 0.3 mg clonidine per day, for one week.

Brief Summary of Prescribing Information

Contraindications: Catapres-TTS* (clonidine) should not be used in patients with known hypersensitivity to clonidine or to any other component of the adhesive layer of the therapeutic system.

Precautions: General: In patients who have developed localized contact sensitization to Catapres-TTS* (clonidine), substitution of oral clonidine hydrochloride therapy may be associated with development of a generalized skin rash.

In patients who develop an allergic reaction to Catapres-TTS* that extends beyond the local patch site (such as generalized skin rash, urticana, or angioedema) oral clonidine hydrochloride substitution may elicit a similar reaction.

As with all antihypertensive therapy, Catapres-TTS* should be used with caution in patients with severe coronary insufficiency, recent myocardial infarction, cerebrovascular disease, or chronic renal failure.

Transdermal clonidine systems should be removed before attempting defibrillation or cardioversion because of the potential for altered electrical conductivity that may enhance the possibility of arcing, a phenomenon associated with the use of defibrillators.

Withdrawal: Patients should be instructed not to discontinue therapy without consulting their physician. Sudden cessation of clonidine treatment has resulted in subjective symptoms such as nervousness, agitation and headache, accompanied or followed by a rapid rise in blood pressure and elevated catecholamine concentrations in the plasma, but such occurrences have usually been associated with previous administration of high oral doses (exceeding 1.2 mg/day) and/or with continuation of concomitant beta-blocker therapy. Rare instances of hypertensive encephalopathy and death have been reported.

An excessive rise in blood pressure following Catapres-TTS* discontinuance can be reversed by administration of oral clonidine or by intravenous phentolamine. If therapy is to be discontinued in patients receiving beta-blockers and clonidine concurrently, beta-blockers should be discontinued several days before cessation of Catapres-TTS* administration.

Perioperative Use: As with oral clonidine therapy, Catapres-TTS* therapy should not be interrupted during the surgical period. Blood pressure should be carefully monitored during surgery and additional measures to control blood pressure should be available if required. Physicians considering starting Catapres-TTS* therapy during the perioperative period must be aware that therapeutic plasma clonidine levels are not achieved until 2 to 3 days after initial application of Catapres-TTS*.

Information for Patients: Patients who engage in potentially hazardous activities, such as operating machinery or driving, should be advised of a potential sedative effect of clonidine. Patients should be cautioned against interruption of Catapres-TTS* therapy without a physician's advice. Patients should be advised that if the system begins to loosen from the skin after application, the adhesive overlay should be applied directly over the system to ensure good adhesion over its 7-day lifetime. Instructions for using the system are provided. Patients who develop moderate or severe erythema and/or localized vesicle formation at the site of application, or a generalized skin rash, should consult their physician promptly about the possible need to remove the patch.

Drug Interactions: If a patient receiving clonidine is also taking tricyclic antidepressants, the effect of clonidine may be reduced, thus necessitating an increase in dosage. Clonidine may enhance the CNS-depressive effects of alcohol, barbiturates or other sedatives. Amitriptyline in combination with clonidine enhances the manifestation of corneal lesions in rats.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In a 132-week (fixed concentration) dietary administration study in rats, clonidine hydrochloride administered at 111 to 160 times the maximum recommended daily human dose (MRDHD) of Catapres-TTS* (clonidine) was unassociated with evidence of carcinogenic potential. Results from the Ames test with clonidine hydrochloride revealed no evidence of mutagenesis. Fertility of male or female rats was unaffected by doses of clonidine hydrochloride as high as 150 mcg/kg or about 10.5 times the MRDHD of Catapres-TTS* (clonidine). Fertility of female rats did, however, appear to be affected (in another experiment) by doses of clonidine hydrochloride at 500 to 2000 mcg/kg or 35 to 140 times the MRDHD of Catapres-TTS* (clonidine).

Pregnancy: Teratogenic Effects. Pregnancy Category C. Reproduction studies performed in rabbits at doses up to approximately 10.5 times the maximum recommended daily human dose (MRDHD) of Catapres-TTS* (clonidine) have revealed no evidence of teratogenic or embryotoxic potential in rabbits. In rats, however, doses as low as 1.2 times the MRDHD of clonidine were associated with increased resorptions in a study in which dams were treated continuously from 2 months prior to mating. Increased resorptions were not associated with treatment at the same or at higher dose levels (up to 10.5 times the MRDHD of clonidine) when dams were treated days 6-15 of gestation. Increased resorptions were observed at much higher levels (140 times the MRDHD of clonidine) in rats and mice treated days 1-14 of gestation (lowest dose employed in that study was 500 mcg/kg). There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers: As clonidine is excreted in human milk, caution should be exercised when Catapres-TTS* (clonidine) is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in children below the age of 12 have not been established.

Adverse Reactions: Most systemic adverse effects during therapy with Catapres-TTS* (clonidine) have been mild and have tended to diminish with continued therapy. In a 3-month, multiclinic trial of Catapres-TTS* in 101 hypertensive patients, the most frequent systemic reactions were dry mouth (25 patients) and drowsiness (12 patients).

Transient localized skin reactions, primarily localized pruritus, occurred in 51 patients. Twenty-six patients experienced localized erythema. This erythema and pruritus were more common in patients utilizing an adhesive overlay for the entire 7-day treatment period. Allergic contact sensitization to Catapres-TTS* was observed in 5 patients.

In additional clinical experience contact dermatitis resulting in treatment discontinuation was observed in 128 of 673 patients (about 19 in 100) after a mean duration of treatment of 37 weeks. The incidence in white females was about 34 in 100; in white males about 18 in 100; in black females about 14 in 100; and in black males about 8 in 100.

The following less frequent adverse experiences were also reported in patients involved in this multiclinic trial with Catapres-TTS*.

Gastrointestinal: Constipation (1 patient); nausea (1); and change in taste (1).

Central Nervous System: Fatigue (6 patients); headache (5); lethargy (3); sedation (3); insomnia (2); dizziness (2); and nervousness (1).

Genitourinary: Impotence/sexual dysfunction (2 patients).

Dermatological: Localized vesiculation (7 patients); hyperpigmentation (5); edema (3); excoriation (3); burning (3); papules (1); throbbing (1); blanching (1); and generalized macular rash (1).

In additional clinical experience involving 3539 patients, less common dermatologic reactions have occurred, where a causal relationship to Catapres-TTS* was not established: maculopapular skin rash (10 cases); urticaria (2 cases); angioedema involving the face (2 cases), one of which also involved the tongue.

Oro-otolaryngeal: Dry throat (2 patients).

In long experience with oral Catapres,* the most common adverse reactions have been dry mouth (about 40%), drowsiness (about 35%) and sedation (about 8%). In addition, the following adverse reactions have been reported less frequently.

Gastrointestinal: Nausea and vomiting, about 5 in 100 patients; anorexia and malaise, each about 1 in 100; mild transient abnormalities in liver function tests, about 1 in 100, parotitis, rarely.

Metabolic: Weight gain, about 1 in 100 patients; gynecomastia, about 1 in 1000; transient elevation of blood glucose or serum creatine phosphokinase, rarely.

Central Nervous System: Nervousness and agitation, about 3 in 100 patients; mental depression, about 1 in 100 and insomnia, about 5 in 1000. Vivid dreams or nightmares, other behavioral changes, restlessness, anxiety, visual and auditory hallucinations and delirium have been reported.

Cardiovascular: Orthostatic symptoms, about 3 in 100 patients; palpitations and tachycardia, and bradycardia, each about 5 in 1000. Raynaud's phenomenon, congestive heart failure, and electrocardiographic abnormalities (i.e. conduction disturbances and arrhythmias) have been reported rarely. Rare cases of sinus bradycardia and atrioventricular block have been reported, both with and without the use of concomitant digitalis.

Dermatological: Rash, about 1 in 100 patients, pruritus, about 7 in 1000; hives, angioneurotic edema and urticaria, about 5 in 1000; alopecia, about 2 in 1000.

Genitourinary: Decreased sexual activity, impotence and loss of libido, about 3 in 100 patients; nocturia, about 1 in 100; difficulty in micturition, about 2 in 1000; urinary retention, about 1 in 1000.

Other: Weakness, about 10 in 100 patients; fatigue, about 4 in 100; headache, and discontinuation syndrome, each about 1 in 100; muscle or joint pain, about 6 in 1000 and cramps of the lower limbs, about 3 in 1000. Dryness, burning of the eyes, dryness of the nasal mucosa, pallor, weakly positive Coombs' test, increased sensitivity to alcohol and fever have been reported.

How Supplied: Catapres-TTS*-1 (clonidine) and Catapres-TTS*-2 are supplied as 4 pouched systems and 4 adhesive overlays per carton, 3 cartons per shipper (NDC 0597-0031-12 and 0597-0032-12, respectively.) Catapres-TTS*-3 is supplied as 4 pouched systems and 4 adhesive overlays per carton (NDC 0597-0033-34).

	Programmed Delivery Clonidine *in vivo* per Day Over 1 Week	Clonidine Content	Size	Code
Catapres-TTS*-1	0.1 mg	2.5 mg	3.5 cm2	BI-31
Catapres-TTS*-2	0.2 mg	5.0 mg	7.0 cm2	BI-32
Catapres-TTS*-3	0.3 mg	7.5 mg	10.5 cm2	BI-33

Consult package insert before prescribing.

Boehringer Ingelheim

Boehringer Ingelheim Pharmaceuticals, Inc.
Ridgefield, CT 06877

CT-BPI-10/86

In Memoriam

Arizona Medical Association

BELSHER, LESLIE J., Scottsdale. Died Jan 19, 1988, aged 50. Graduate of Stanford University School of Medicine, Stanford, California, 1966. Licensed in Arizona in 1980. Dr Belsher was a member of the Maricopa County Medical Society.

KOLLAR, EDWARD J., Tucson. Died Dec 12, 1987, aged 69. Graduate of University of Illinois College of Medicine, Chicago, 1945. Licensed in Arizona in 1962. Dr Kollar was a member of the Pima County Medical Society.

SMITH, ROBERT GOODRICH, Sun City. Died Jan 23, 1988, aged 81. Graduate of Ohio State University College of Medicine, Columbus, 1931. Licensed in Arizona in 1981.

THOMAS, WILLIAM J., Flagstaff. Died Dec 23, 1987, aged 57. Graduate of University of Virginia School of Medicine, Charlottesville, 1956. Licensed in Arizona in 1963. Dr Thomas was a member of the Coconino County Medical Society.

California Medical Association

BLACK, JET R., Fullerton. Died Dec 1987, aged 54. Graduate of University of California, Irvine, 1967. Dr Black was a member of the Orange County Medical Association.

BRISBIN, ROBERT LEE, San Diego. Died Dec 1, 1987, aged 57. Graduate of University of Wisconsin Medical School, Madison, 1955. Dr Brisbin was a member of the San Diego County Medical Society.

CHISHOLM, COLIN B., San Clemente. Died Sep 25, 1987, aged 83. Graduate of McGill University Faculty of Medicine, Montreal, Quebec, 1929. Licensed in California in 1947. Dr Chisholm was a member of the Orange County Medical Association.

CLARK, STEPHEN H., Buena Park. Died Oct 17, 1987, aged 68. Licensed in California in 1954. Dr Clark was a member of the Orange County Medical Association.

DANIELS, FRANCIS R., Santa Ana. Died Oct 20, 1987, aged 87. Graduate of State University of New York at Buffalo, 1924. Licensed in California in 1955. Dr Daniels was a member of the Orange County Medical Association.

FENLON, ROBERTA F., San Francisco. Died Aug 31, 1987, aged 76. Graduate of University of Iowa, Iowa City. Licensed in California in 1943. Dr Fenlon was a member of the San Francisco Medical Society.

FERNANDES, DAVID A., El Cerrito. Died Oct 25, 1987, aged 78. Graduate of Medical School of Dutch Guyana, 1932, and University of Leiden, 1935. Licensed in California in 1950. Dr Fernandes was a member of the Alameda-Contra Costa Medical Association.

(Continued on Page 414)

"Living in the city is lonely enough... with herpes it's like solitary confinement."
ZOVIRAX®
(acyclovir)
CAPSULES
Prevent genital herpes recurrences month after month with daily therapy.
(In controlled studies, recurrences were totally prevented for 4 to 6 months in up to 75% of patients.)
Please see last page of this advertisement for brief summary of prescribing information.

ZOVIRAX® (acyclovir) CAPSULES

Help free your patients from recurrences.

Daily therapy

Coping with genital herpes is rarely easy. For some, the worst part is the pain and discomfort of frequent attacks — month after month, year after year. For others, the emotional burden presents a more difficult problem, leading to social isolation, anxiety, and diminished self-esteem.

Prevent or reduce recurrences

Although your patients have to live with herpes, they shouldn't have to suffer. Daily therapy with ZOVIRAX CAPSULES can help free them from the cycle of recurrent genital herpes. For many, one capsule three times a day can suppress recurrences completely while on therapy.

Generally well tolerated

Daily therapy with ZOVIRAX CAPSULES is generally well tolerated. The most frequent adverse reactions reported during clinical trials were headache, diarrhea, nausea/vomiting, vertigo, and arthralgia.

The physical and emotional difficulties posed by genital herpes are unique for each patient. The frequency and severity of recurrent episodes, as well as the emotional impact of the disease, should be considered when selecting daily therapy with ZOVIRAX CAPSULES.

Please see brief summary of prescribing information on next page.

Prevent recurrences month after month*

ZOVIRAX® (acyclovir) CAPSULES

Brief Summary

INDICATIONS AND USAGE: Zovirax Capsules are indicated for the treatment of initial episodes and the management of recurrent episodes of genital herpes in certain patients.

The severity of disease is variable depending upon the immune status of the patient, the frequency and duration of episodes, and the degree of cutaneous or systemic involvement. These factors should determine patient management, which may include symptomatic support and counseling only, or the institution of specific therapy. The physical, emotional and psycho-social difficulties posed by herpes infections as well as the degree of debilitation, particularly in immunocompromised patients, are unique for each patient, and the physician should determine therapeutic alternatives based on his or her understanding of the individual patient's needs. Thus Zovirax Capsules are not appropriate in treating all genital herpes infections. The following guidelines may be useful in weighing the benefit/risk considerations in specific disease categories:

First Episodes (primary and nonprimary infections — commonly known as initial genital herpes):

Double-blind, placebo-controlled studies have demonstrated that orally administered Zovirax significantly reduced the duration of acute infection (detection of virus in lesions by tissue culture) and lesion healing. The duration of pain and new lesion formation was decreased in some patient groups. The promptness of initiation of therapy and/or the patient's prior exposure to Herpes simplex virus may influence the degree of benefit from therapy. Patients with mild disease may derive less benefit than those with more severe episodes. In patients with extremely severe episodes, in which prostration, central nervous system involvement, urinary retention or inability to take oral medication require hospitalization and more aggressive management, therapy may be best initiated with intravenous Zovirax.

Recurrent Episodes:

Double-blind, placebo-controlled studies in patients with frequent recurrences (6 or more episodes per year) have shown that Zovirax Capsules given for 4 to 6 months prevented or reduced the frequency and/or severity of recurrences in greater than 95% of patients. Clinical recurrences were prevented in 40 to 75% of patients. Some patients experienced increased severity of the first episode following cessation of therapy; the severity of subsequent episodes and the effect on the natural history of the disease are still under study.

The safety and efficacy of orally administered acyclovir in the suppression of frequent episodes of genital herpes have been established only for up to 6 months. Chronic suppressive therapy is most appropriate when, in the judgement of the physician, the benefits of such a regimen outweigh known or potential adverse effects. In general, Zovirax Capsules should not be used for the suppression of recurrent disease in mildly affected patients. Unanswered questions concerning the human relevance of *in vitro* mutagenicity studies and reproductive toxicity studies in animals given very high doses of acyclovir for short periods (see Carcinogenesis, Mutagenesis, Impairment of Fertility) should be borne in mind when designing long-term management for individual patients. Discussion of these issues with patients will provide them the opportunity to weigh the potential for toxicity against the severity of their disease. Thus, this regimen should be considered only for appropriate patients and only for six months until the results of ongoing studies allow a more precise evaluation of the benefit/risk assessment of prolonged therapy.

Limited studies have shown that there are certain patients for whom intermittent short-term treatment of recurrent episodes is effective. This approach may be more appropriate than a suppressive regimen in patients with infrequent recurrences.

Immunocompromised patients with recurrent herpes infections can be treated with either intermittent or chronic suppressive therapy. Clinically significant resistance, although rare, is more likely to be seen with prolonged or repeated therapy in severely immunocompromised patients with active lesions.

CONTRAINDICATIONS: Zovirax Capsules are contraindicated for patients who develop hypersensitivity or intolerance to the components of the formulation.

WARNINGS: Zovirax Capsules are intended for oral ingestion only.

PRECAUTIONS: General: Zovirax has caused decreased spermatogenesis at high doses in some animals and mutagenesis in some acute studies at high concentrations of drug (see PRECAUTIONS — Carcinogenesis, Mutagenesis, Impairment of Fertility). The recommended dosage and length of treatment should not be exceeded (see DOSAGE AND ADMINISTRATION).

Exposure of Herpes simplex isolates to acyclovir *in vitro* can lead to the emergence of less sensitive viruses. The possibility of the appearance of less sensitive viruses in man must be borne in mind when treating patients. The relationship between the *in vitro* sensitivity of Herpes simplex virus to acyclovir and clinical response to therapy has yet to be established.

Because of the possibility that less sensitive virus may be selected in patients who are receiving acyclovir, all patients should be advised to take particular care to avoid potential transmission of virus if active lesions are present while they are on therapy. In severely immunocompromised patients, the physician should be aware that prolonged or repeated courses of acyclovir may result in selection of resistant viruses which may not fully respond to continued acyclovir therapy.

Drug Interactions: Co-administration of probenecid with intravenous acyclovir has been shown to increase the mean half-life and the area under the concentration-time curve. Urinary excretion and renal clearance were correspondingly reduced.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Acyclovir was tested in lifetime bioassays in rats and mice at single daily doses of 50, 150 and 450 mg/kg given by gavage. There was no statistically significant difference in the incidence of tumors between treated and control animals, nor did acyclovir shorten the latency of tumors. In 2 *in vitro* cell transformation assays, used to provide preliminary assessment of potential oncogenicity in advance of these more definitive life-time bioassays in rodents, conflicting results were obtained. Acyclovir was positive at the highest dose used in one system and the resulting morphologically transformed cells formed tumors when inoculated into immunosuppressed, syngeneic, weanling mice. Acyclovir was negative in another transformation system considered less sensitive.

In acute studies, there was an increase, not statistically significant, in the incidence of chromosomal damage at maximum tolerated parenteral doses of 100 mg/kg acyclovir in rats but not Chinese hamsters; higher doses of 500 and 1000 mg/kg were clastogenic in Chinese hamsters. In addition, no activity was found after 5 days dosing in a dominant lethal study in mice. In 6 of 11 microbial and mammalian cell assays, no evidence of mutagenicity was observed. At 3 loci in a Chinese hamster ovary cell line, the results were inconclusive. In 2 mammalian cell assays (human lymphocytes and L5178Y mouse lymphoma cells *in vitro*), positive responses for mutagenicity and chromosomal damage occurred, but only at concentrations at least 400 times the acyclovir plasma levels achieved in man.

Acyclovir has not been shown to impair fertility or reproduction in mice (450 mg/kg/day, p.o.) or in rats (25 mg/kg/day, s.c.). At 50 mg/kg/day s.c. in the rat, there was a statistically significant increase in post-implantation loss, but no concomitant decrease in litter size. In female rabbits treated subcutaneously with acyclovir subsequent to mating, there was a statistically significant decrease in implantation efficiency but no concomitant decrease in litter size at a dose of 50 mg/kg/day. No effect upon implantation efficiency was observed when the same dose was administered intravenously. In a rat peri- and postnatal study at 50 mg/kg/day s.c., there was a statistically significant decrease in the group mean numbers of corpora lutea, total implantation sites and live fetuses in the F_1 generation. Although not statistically significant, there was also a dose related decrease in group mean numbers of live fetuses and implantation sites at 12.5 mg/kg/day and 25 mg/kg/day, s.c. The intravenous administration of 100 mg/kg/day, a dose known to cause obstructive nephropathy in rabbits, caused a significant increase in fetal resorptions and a corresponding decrease in litter size. However, at a maximum tolerated intravenous dose of 50 mg/kg/day in rabbits, there were no drug-related reproductive effects.

Intraperitoneal doses of 320 or 80 mg/kg/day acyclovir given to rats for 1 and 6 months, respectively, caused testicular atrophy. Testicular atrophy was persistent through the 4-week postdose recovery phase after 320 mg/kg/day; some evidence of recovery of sperm production was evident 30 days postdose. Intravenous doses of 100 and 200 mg/kg/day acyclovir given to dogs for 31 days caused aspermatogenesis. Testicles were normal in dogs given 50 mg/kg/day, i.v. for one month.

Pregnancy: *Teratogenic Effects:* Pregnancy Category C. Acyclovir was not teratogenic in the mouse (450 mg/kg/day, p.o.), rat (50 mg/kg/day, s.c.) or rabbit (50 mg/kg/day, s.c. and i.v.). There are no adequate and well-controlled studies in pregnant women. Acyclovir should not be used during pregnancy unless the potential benefit justifies the potential risk to the fetus. Although acyclovir was not teratogenic in animal studies, the drug's potential for causing chromosome breaks at high concentration should be taken into consideration in making this determination.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Zovirax is administered to a nursing woman. In nursing mothers, consideration should be given to not using acyclovir treatment or discontinuing breastfeeding.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS — Short-Term Administration: The most frequent adverse reactions reported during clinical trials were nausea and/or vomiting in 8 of 298 patient treatments (2.7%) and headache in 2 of 298 (0.6%). Less frequent adverse reactions, each of which occurred in 1 of 298 patient treatments (0.3%), included diarrhea, dizziness, anorexia, fatigue, edema, skin rash, leg pain, inguinal adenopathy, medication taste and sore throat.

Long-Term Administration: The most frequent adverse reactions reported in studies of daily therapy for 3 to 6 months were headache in 33 of 251 patients (13.1%), diarrhea in 22 of 251 (8.8%), nausea and/or vomiting in 20 of 251 (8.0%), vertigo in 9 of 251 (3.6%), and arthralgia in 9 of 251 (3.6%). Less frequent adverse reactions, each of which occurred in less than 3% of the 251 patients (see number of patients in parentheses), included skin rash (7), insomnia (4), fatigue (7), fever (4), palpitations (1), sore throat (2), superficial thrombophlebitis (1), muscle cramps (2), pars planitis (1), menstrual abnormality (4), acne (3), lymphadenopathy (2), irritability (1), accelerated hair loss (1), and depression (1).

DOSAGE AND ADMINISTRATION: Treatment of initial genital herpes: One 200 mg capsule every 4 hours, while awake, for a total of 5 capsules daily for 10 days (total 50 capsules).

Chronic suppressive therapy for recurrent disease: One 200 mg capsule 3 times daily for up to 6 months. Some patients may require more drug, up to one 200 mg capsule 5 times daily for up to 6 months.

Intermittent Therapy: One 200 mg capsule every 4 hours, while awake, for a total of 5 capsules daily for 5 days (total 25 capsules). Therapy should be initiated at the earliest sign or symptom (prodrome) of recurrence.

Patients With Acute or Chronic Renal Impairment: One 200 mg capsule every 12 hours is recommended for patients with creatinine clearance $\leq$10 ml/min/1.73/m^2.

HOW SUPPLIED: Zovirax Capsules (blue, opaque) containing 200 mg acyclovir and printed with "Wellcome ZOVIRAX 200" - Bottles of 100 (NDC-0081-0991-55) and unit dose pack of 100 (NDC-0081-0991-56).

Store at 15°-30°C (59°-86°F) and protect from light.

*In controlled studies, recurrences were totally prevented for 4 to 6 months in up to 75% of patients.

Burroughs Wellcome Co., Research Triangle Park, North Carolina 27709

IMPROVING LIVES THROUGH ANTIVIRAL RESEARCH

BURROUGHS WELLCOME CO

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WHEN ACID REFLUX ERUPTS

Zantac dramatically lessens pain of acid reflux[1] by inhibiting the formation of acid at its source–an action unique among pharmaceutical agents indicated for the treatment of gastroesophageal reflux disease.

Zantac® *Tablets*

ranitidine HCl/Glaxo 150 mg tablets bid

The only H_2-antagonist indicated for the treatment of gastroesophageal reflux disease

1 Sontag S, Robinson M, McCallum R, et al. Ranitidine therapy for gastroesophageal reflux disease. Results of a large double-blind trial. *Arch Intern Med* 1987; 147:1485-1491.

See next page for Brief Summary of Product Information.

Glaxo/ ROCHE

ZANTAC® 150 Tablets
(ranitidine hydrochloride)
ZANTAC® 300 Tablets
(ranitidine hydrochloride)

BRIEF SUMMARY

The following is a brief summary only. Before prescribing, see complete prescribing information in ZANTAC® product labeling.

INDICATIONS AND USAGE: ZANTAC® is indicated in:
1. Short-term treatment of **active duodenal ulcer.** Most patients heal within four weeks.
2. **Maintenance therapy** for duodenal ulcer patients at reduced dosage after healing of acute ulcers.
3. The treatment of **pathological hypersecretory conditions** (eg, Zollinger-Ellison syndrome and systemic mastocytosis).
4. Short-term treatment of **active, benign gastric ulcer.** Most patients heal within six weeks and the usefulness of further treatment has not been demonstrated.
5. Treatment of **gastroesophageal reflux disease (GERD).** Symptomatic relief commonly occurs within one or two weeks after starting therapy. Therapy for longer than six weeks has not been studied.

In active duodenal ulcer, active, benign gastric ulcer, hypersecretory states, and GERD, concomitant antacids should be given as needed for relief of pain.

CONTRAINDICATIONS: ZANTAC® is contraindicated for patients known to have hypersensitivity to the drug.

PRECAUTIONS: General: 1. Symptomatic response to ZANTAC® therapy does not preclude the presence of gastric malignancy.

2. Since ZANTAC is excreted primarily by the kidney, dosage should be adjusted in patients with impaired renal function (see **DOSAGE AND ADMINISTRATION**). Caution should be observed in patients with hepatic dysfunction since ZANTAC is metabolized in the liver.

Laboratory Tests: False-positive tests for urine protein with Multistix® may occur during ZANTAC therapy, and therefore testing with sulfosalicylic acid is recommended.

Drug Interactions: Although ZANTAC has been reported to bind weakly to cytochrome P-450 in vitro, recommended doses of the drug do not inhibit the action of the cytochrome P-450-linked oxygenase enzymes in the liver. However, there have been isolated reports of drug interactions which suggest that ZANTAC may affect the bioavailability of certain drugs by some mechanism as yet unidentified (eg, a pH-dependent effect on absorption or a change in volume of distribution).

Carcinogenesis, Mutagenesis, Impairment of Fertility: There was no indication of tumorigenic or carcinogenic effects in lifespan studies in mice and rats at doses up to 2,000 mg/kg/day.

Ranitidine was not mutagenic in standard bacterial tests (*Salmonella, E. coli*) for mutagenicity at concentrations up to the maximum recommended for these assays.

In a dominant lethal assay, a single oral dose of 1,000 mg/kg to male rats was without effect on the outcome of two matings per week for the next nine weeks.

Pregnancy: ***Teratogenic Effects: Pregnancy Category B:*** Reproduction studies have been performed in rats and rabbits at doses up to 160 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to ZANTAC. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers: ZANTAC is secreted in human milk. Caution should be exercised when ZANTAC is administered to a nursing mother.

Pediatric Use: Safety and effectiveness in children have not been established.

Use in Elderly Patients: Ulcer healing rates in elderly patients (65 to 82 years of age) were no different from those in younger age groups. The incidence rates for adverse events and laboratory abnormalities were also not different from those seen in other age groups.

ADVERSE REACTIONS: The following have been reported as events in clinical trials or in the routine management of patients treated with oral ZANTAC®. The relationship to ZANTAC therapy has been unclear in many cases. Headache, sometimes severe, seems to be related to ZANTAC administration.

Central Nervous System: Rarely, malaise, dizziness, somnolence, insomnia, and vertigo. Rare cases of reversible mental confusion, agitation, depression, and hallucinations have been reported, predominantly in severely ill elderly patients. Rare cases of reversible blurred vision suggestive of a change in accommodation have been reported.

Cardiovascular: Rare reports of tachycardia, bradycardia, and premature ventricular beats.

Gastrointestinal: Constipation, diarrhea, nausea/vomiting, and abdominal discomfort/pain.

Hepatic: In normal volunteers, SGPT values were increased to at least twice the pretreatment levels in 6 of 12 subjects receiving 100 mg qid IV for seven days, and in 4 of 24 subjects receiving 50 mg qid IV for five days. With oral administration there have been occasional reports of reversible hepatitis, hepatocellular or hepatocanalicular or mixed, with or without jaundice.

Musculoskeletal: Rare reports of arthralgias.

Hematologic: Reversible blood count changes (leukopenia, granulocytopenia, thrombocytopenia) have occurred in a few patients. Rare cases of agranulocytosis or of pancytopenia, sometimes with marrow hypoplasia, have been reported.

Endocrine: Controlled studies in animals and man have shown no stimulation of any pituitary hormone by ZANTAC (ranitidine hydrochloride) and no antiandrogenic activity, and cimetidine-induced gynecomastia and impotence in hypersecretory patients have resolved when ZANTAC has been substituted. However, occasional cases of gynecomastia, impotence, and loss of libido have been reported in male patients receiving ZANTAC, but the incidence did not differ from that in the general population.

Integumentary: Rash, including rare cases suggestive of mild erythema multiforme, and rarely, alopecia.

Other: Rare cases of hypersensitivity reactions (eg, bronchospasm, fever, rash, eosinophilia) and small increases in serum creatinine.

OVERDOSAGE: Information concerning possible overdosage and its treatment appears in the full prescribing information.

DOSAGE AND ADMINISTRATION: Active Duodenal Ulcer: The current recommended adult oral dosage is 150 mg twice daily. An alternate dosage of 300 mg once daily at bedtime can be used for patients in whom dosing convenience is important. The advantages of one treatment regimen compared to the other in a particular patient population have yet to be demonstrated.

Maintenance Therapy: The current recommended adult oral dosage is 150 mg at bedtime.

Pathological Hypersecretory Conditions (such as Zollinger-Ellison syndrome): The current recommended adult oral dosage is 150 mg twice a day. In some patients it may be necessary to administer ZANTAC® 150-mg doses more frequently. Doses should be adjusted to individual patient needs, and should continue as long as clinically indicated. Doses up to 6 g/day have been employed in patients with severe disease.

Benign Gastric Ulcer: The current recommended adult oral dosage is 150 mg twice a day.

GERD: The current recommended adult oral dosage is 150 mg twice a day.

Dosage Adjustment for Patients with Impaired Renal Function: On the basis of experience with a group of subjects with severely impaired renal function treated with ZANTAC, the recommended dosage in patients with a creatinine clearance less than 50 ml/min is 150 mg every 24 hours. Should the patient's condition require, the frequency of dosing may be increased to every 12 hours or even further with caution. Hemodialysis reduces the level of circulating ranitidine. Ideally, the dosage schedule should be adjusted so that the timing of a scheduled dose coincides with the end of hemodialysis.

HOW SUPPLIED: ZANTAC® 300 Tablets (ranitidine hydrochloride equivalent to 300 mg of ranitidine) are yellow, capsule-shaped tablets embossed with "ZANTAC 300" on one side and "Glaxo" on the other. They are available in bottles of 30 (NDC 0173-0393-40) and unit dose packs of 100 tablets (NDC 0173-0393-47).

ZANTAC® 150 Tablets (ranitidine hydrochloride equivalent to 150 mg of ranitidine) are white tablets embossed with "ZANTAC 150" on one side and "Glaxo" on the other. They are available in bottles of 60 tablets (NDC 0173-0344-42) and unit dose packs of 100 tablets (NDC 0173-0344-47).

Store between 15° and 30°C (59° and 86°F) in a dry place. Protect from light. Replace cap securely after each opening.

August 1987

Glaxo

Glaxo Inc
Research Triangle Park, NC 27709

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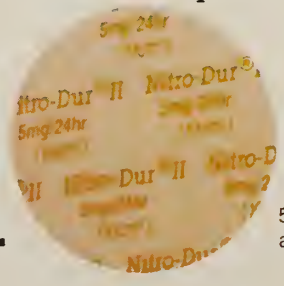

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Please see next page for brief summary of prescribing information.

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(nitroglycerin)
Transdermal Infusion System

- **Easy opening—even for arthritic hands.**
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When prescribing Nitro-Dur II, you should write your prescription using the Roman numeral designation II to identify the product. This should be followed by the appropriate dosage strength in mg/24 hours. Thus, any confusion that may arise between product names and/or dosage strengths prescribed will be avoided.

BRIEF SUMMARY

INDICATIONS AND USAGE: This drug product has been conditionally approved by the FDA for the prevention and treatment of angina pectoris due to coronary artery disease. The conditional approval reflects a determination that the drug may be marketed while further investigation of its effectiveness is undertaken. A final evaluation of the effectiveness of the product will be announced by the FDA.

CONTRAINDICATIONS: Intolerance of organic nitrate drugs, marked anemia.

WARNINGS: The NITRO-DUR II system should be used under careful clinical and/or hemodynamic monitoring in patients with acute myocardial infarction or congestive heart failure.

In terminating treatment of anginal patients, both the dosage and frequency of application must be gradually reduced over a period of 4 to 6 weeks in order to prevent sudden withdrawal reactions, which are characteristic of all vasodilators in the nitroglycerin class.

PRECAUTIONS: Symptoms of hypotension, such as faintness, weakness or dizziness, particularly orthostatic hypotension, may be due to overdosage. If during the course of treatment these symptoms occur, the dosage should be reduced or use of the product discontinued. NITRO-DUR II is not intended for use in the treatment of acute anginal attacks. For this purpose, occasional use of sublingual nitroglycerin may be necessary.

Pregnancy: Pregnancy Category C. Animal reproduction studies have not been conducted with NITRO-DUR II. It is also not known whether nitroglycerin can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Nitroglycerin should be given to a pregnant woman only if clearly needed.

Nursing Mothers: It is not known whether nitroglycerin is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when NITRO-DUR II is administered to a nursing woman.

ADVERSE REACTIONS: Transient headache is the most common side effect, especially when higher doses of the drug are administered. Headaches should be treated with mild analgesics while continuing NITRO-DUR II therapy. If headache persists, the NITRO-DUR II dosage should be reduced or use of the product discontinued.

Adverse reactions reported less frequently include hypotension, increased heart rate, faintness, flushing, dizziness, nausea, vomiting, and dermatitis. Except for dermatitis, these symptoms are attributed to the pharmacologic effects of nitroglycerin. However, they may be symptoms of overdosage. When they persist, the NITRO-DUR II dosage should be reduced or use of the product discontinued.

CAUTION: Federal law prohibits dispensing without prescription. For complete prescribing information, please see package insert.

EDP #I030150 Revised 0585

All transdermal nitroglycerin products are being marketed pending final evaluation of effectiveness by the FDA.

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Kenilworth, NJ 07033 USA
World leader in drug delivery systems.

ND-2101/14440402

In Memoriam

(Continued from Page 406)

Hoversten, Lester T., San Jose. Died Oct 22, 1987, aged 75. Graduate of California College of Medicine, 1948. Dr Hoversten was a member of the Santa Clara County Medical Society.

Johnson, Thomas P., San Diego. Died Oct 13, 1987, aged 52. Graduate of University of Minnesota, 1960. Licensed in California in 1961. Dr Johnson was a member of the San Diego County Medical Society.

Kaplan, Charles B., Anaheim. Died Sep 7, 1987, aged 61. Graduate of University of Illinois College of Medicine, 1951. Licensed in California in 1955. Dr Kaplan was a member of the Orange County Medical Association.

Miller, John N., Jr, Sacramento. Died Nov 13, 1987, aged 60. Graduate of University of California, San Francisco, School of Medicine. Licensed in California in 1950. Dr Miller was a member of the Sacramento-El Dorado Medical Society.

Oronzi, Vincent, Novato. Died Jan 9, 1988, aged 44. Graduate of New York Medical College, Valhalla, 1968. Dr Oronzi was a member of the Marin Medical Society.

Robinson, Howard D., Redwood City. Died Nov 7, 1987, aged 54. Graduate of University of Michigan Medical School, Ann Arbor, 1957. Licensed in California in 1961. Dr Robinson was a member of the San Mateo County Medical Society.

Shipley, Barbara B., Santa Cruz. Died Sep 23, 1987, aged 63. Graduate of Woman's Medical College of Pennsylvania, 1957. Licensed in California in 1959. Dr Shipley was a member of the Santa Cruz County Medical Society.

Thibault, Hector H., Los Gatos. Died Oct 17, 1987, aged 67. Graduate of Georgetown University School of Medicine, Washington, DC, 1944. Licensed in California in 1953. Dr Thibault was a member of the Santa Clara County Medical Society.

Thompson, Claude V., Lodi. Died Oct 29, 1987, aged 92. Licensed in California in 1921. Dr Thompson was a member of the San Joaquin County Medical Society.

Treadwell, Richard T., San Luis Obispo. Died Jan 1, 1988, aged 91. Graduate of Rush Medical College, Chicago, 1922. Licensed in California in 1942. Dr Treadwell was a member of the San Luis Obispo County Medical Society.

Vaughan, John E., Bakersfield. Died Jan 18, 1988, aged 81. Graduate of University of Virginia School of Medicine, Charlottesville, 1933. Licensed in California in 1936. Dr Vaughan was a member of the Kern County Medical Society.

Ziegler, Dillman Forbes, Vacaville. Died Sep 15, 1987, aged 75. Graduate of University of Illinois College of Medicine, Chicago, 1938. Licensed in California in 1947. Dr Ziegler was a member of the Humboldt-Del Norte Medical Society.

Utah Medical Association

Daines, William P., Ogden. Died Nov 7, 1987, aged 69. Graduate of Northwestern University Medical School, Chicago, 1943. Licensed in Utah in 1949. Dr Daines was a member of the Weber County Medical Society.

Dituri, Bessie, Salt Lake City. Died Oct 24, 1987, aged 64. Graduate of University of Pennsylvania School of Medicine, Philadelphia. Dr Dituri was a member of the Salt Lake County Medical Society.

Dituri, Frank, Salt Lake City. Died Oct 17, 1987, aged 67. Graduate of University of Pennsylvania School of Medicine, Philadelphia. Licensed in Utah in 1972. Dr Dituri was a member of the Salt Lake County Medical Society.

WHY AMA?

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ARIZONA

The following list of continuing medical education programs in Arizona is compiled by the Arizona Medical Association. All courses listed have been certified as meeting the criteria for Category I of the ArMA CME Certificate and the AMA Physicians Recognition Award. To list Category I continuing medical education programs, please send information to Arizona Medical Association, 810 West Bethany Home Road, Phoenix, AZ 85013; or phone (602) 246-8901.

Brochures and registration forms are available from the contact person or organization sponsoring the program.

April 30—**Medical and Psychological Perspectives of Post-Polio Sequelae.** Ramada Inn Airport North, Phoenix. Sat. Contact: Pat Caldwell, Arizona Easter Seal Society, (602) 252-6061.

June 9—**Arizona Medical Association Annual Scientific Session.** Loews Ventana Canyon Resort, Tucson. Thurs. Contact: ArMA.

PATHOLOGY

May 14-15—**Selected Topics in Gynecologic Pathology.** Arizona Society of Pathologists and U of A at Westward Look Resort, Tucson. Sat-Sun. 7 hrs. Contact: Beverly Richter, Arizona Society of Pathologists, 810 W Bethany Home Rd, Phoenix 85013. (602) 246-8901.

CONTACT INFORMATION

ArMA—Contact: Arizona Medical Association, 810 W Bethany Home Rd, Phoenix, AZ 85013. (602) 246-8901.

U of A—Contact: University of Arizona College of Medicine, Arizona Health Sciences Center, Tucson, AZ 85724. (602) 626-6707.

CALIFORNIA, HAWAII AND NEVADA

This listing of continuing education programs in California, Hawaii and Nevada is supplied by the Committee on Continuing Medical Education of the California Medical Association. All courses and meetings listed have been approved for Category I credit toward the CMA Certificate in Continuing Medical Education. To have accredited courses listed here, please send information at least two months in advance to Department of Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690; or phone (415) 863-5522. For a list of organizations approved for Category I credit toward the CMA Certificate in Continuing Medical Education or for more information on accreditation or certification, please write to the above address.

ANESTHESIOLOGY

May 15-20—**Hawaiian Seminar on Clinical Anesthesia.** California Society of Anesthesiologists at Sheraton Kauai Hotel, Poipu Beach, Kauai. Sun-Fri. 20 hrs. $325-375. Contact: California Society of Anesthesiologists, 1065 Hillsdale Blvd, #410, Foster City 94404. (415) 345-3020.

May 16-20—**5th International Symposium: Computing in Anesthesia and Intensive Care.** UCSD at US Grant Hotel, San Diego. Mon-Fri. 20 hrs. $300. Contact: UCSD.

June 16-19—**California Society of Anesthesiologists 1988 Annual Meeting** at Marriott Hotel, Anaheim. Thurs-Sun. 16 hrs. $150-225. Contact: California Society of Anesthesiologists, 1065 Hillsdale Blvd, #410, Foster City 94404. (415) 345-3020.

August 21-27—**Hawaiian Seminar on Clinical Anesthesia.** California Society of Anesthesiologists at Inter-Continental Hotel, Wailea, Maui. Sun-Sat. 20 hrs. $325/$375. Contact: CSA, 1065 E. Hilldale Blvd, Suite 410, Foster City 94404. (415) 345-3020.

October 16-21—**Hawaiian Seminar on Clinical Anesthesia.** California Society of Anesthesiologists at Westin Maui Hotel, Maui. Sun-Fri. 20 hrs. $325/$375. Contact: CSA, 1065 Hilldale Blvd, Suite 410, Foster City 94404. (415) 345-3020.

CARDIOLOGY

April 15-17—**Coronary Artery Disease: A Commemorative Symposium—75 Years Since Anitschkow and Herrick.** UCSF. Contact: UCSF.

April 18-27—**Cardiology for the Consultant.** Scripps Clinic and Research Foundation at the Inn at Rancho Santa Fe, Rancho Santa Fe. Mon-Wed. 40 hrs. $900. Contact: Bonny Mower, 10666 N. Torrey Pines Road, La Jolla, 92037. (619) 457-8556.

April 24—**Cardiology Symposium 1988.** Inter-Community Medical Center at Industry Hills & Sheraton Resort, City of Industry. Sun. $100. Contact: Inter-Community Medical Center, Dept. of Education. (818) 915-6242.

KEY TO ABBREVIATIONS

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690. (415) 863-5522.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Herbert M. Thomas, MD, MPH, Director of CME, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th Street, Los Angeles 90059. (213) 603-3183.

LLU: Loma Linda University
Contact: Varner J. Johns, Jr, MD, Associate Dean for Continuing Medical Education, Loma Linda University School of Medicine, Loma Linda 92354. (714) 796-7311, ext 2400.

PMC: Pacific Medical Center
Contact: Continuing Education, Pacific Medical Center, PO Box 7999, San Francisco 94120. (415) 563-4321, ext 2761.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Medical School Office Building, Suite X-365, Stanford 94305-6114. (415) 723-5594.

UCD: University of California, Davis
Contact: Ruth Feryok, Director, Office of Continuing Medical Education, University of California, Davis, School of Medicine, 2701 Stockton Boulevard, Sacramento 95817. (916) 453-5390.

UCI: University of California, Irvine
Contact: Melvin I. Marks, MD, Assistant Dean, University of California, Irvine, California College of Medicine, c/o UCI/CME Program, Memorial Medical Center, 2801 Atlantic Avenue, Long Beach 90801-1428. (213) 595-3811, or (714) 856-5414, UCI Extension.

UCLA: University of California, Los Angeles
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, PO Box 24902, UCLA, Los Angeles 90024. (213) 825-7241.

UCSD: University of California, San Diego
Contact: Office of Continuing Medical Education, University of California, San Diego, School of Medicine (M-017), La Jolla 92093. (619) 534-3713.

UCSF: University of California, San Francisco
Contact: Robert Maggio, Administrative Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 476-4251.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 1975 Zonal Ave, KAM314, Los Angeles 90033. (213) 224-7051.

(Continued on Page 418)

The portrait of anxiety

Upjohn The Upjohn Company
Kalamazoo, Michigan 49001 USA

Please see adjacent page for brief summary of prescribing information.

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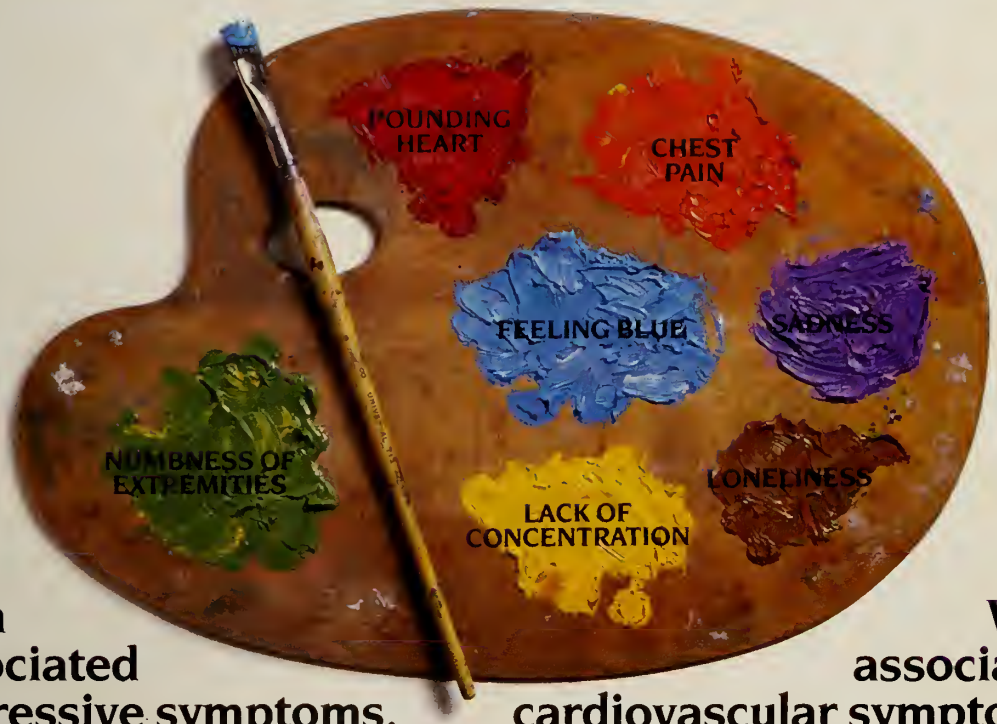
is often complicated



With associated depressive symptoms.

In double-blind, four-week clinical trials in 632 patients with moderate to severe anxiety, therapy with XANAX was compared with placebo.

XANAX was significantly more effective ($P<.001$) than placebo in relieving the anxiety, with over half of the patients showing marked to moderate improvement by the first evaluation period (one week).

In addition, over 70% of these patients experienced associated moderate to severe depressed mood. XANAX was shown to be significantly more effective ($P<.014$) than placebo in improving the associated depressed mood.

With associated cardiovascular symptoms.

Almost 60% of patients in the study had anxiety with associated cardiovascular symptoms even though cardiovascular disease had been ruled out. XANAX was shown to effectively relieve anxiety including the associated cardiovascular symptoms.

XANAX, the first of a unique class—the triazolobenzodiazepines.

- *Well tolerated*—Side effects, if they occur, are generally observed at the beginning of therapy and usually disappear with continued medication. Drowsiness and light-headedness were the most commonly reported adverse reactions.
- *Sustained efficacy*—No reported increase in dosage during 16-week clinical study, once an appropriate dosage was achieved. Since long-term effectiveness of XANAX has not been established, it is recommended that it not be used for longer than 16 weeks.
- *Simple dosage*—0.25 to 0.5 mg t.i.d.

TABLETS 0.25, 0.5 & 1 MG

Xanax®

alprazolam IV

for the relief of complicated anxiety

XANAX® Tablets
(alprazolam) C

CONTRAINDICATIONS
Patients with sensitivity to this drug or other benzodiazepines and in acute narrow angle glaucoma

WARNINGS
Not of value in psychotic patients. Caution patients against hazardous occupations requiring complete mental alertness and about the simultaneous ingestion of alcohol and other CNS depressant drugs.

Benzodiazepines can cause fetal harm in pregnant women. Warn patients of the potential hazard to the fetus. Avoid during the first trimester.

PRECAUTIONS
General: The dosage of XANAX Tablets should be reduced or withdrawn gradually, since withdrawal seizures have been reported upon abrupt withdrawal. If XANAX is combined with other psychotropics or anticonvulsant drugs, consider drug potentiation (see Drug Interaction section). Exercise the usual precautions regarding size of the prescription for depressed or suicidal patients. In elderly and debilitated patients, use the lowest possible dosage (see Dosage and Administration). Observe the usual precautions in treating patients with impaired renal or hepatic function.

Information for Patients: Alert patients about: (a) consumption of alcohol and drugs, (b) possible fetal abnormalities, (c) operating machinery or driving, (d) not increasing dose of the drug due to risk of dependence, (e) not stopping the drug abruptly. *Laboratory Tests:* Not ordinarily required in otherwise healthy patients. *Drug Interactions:* Additive CNS depressant effects with other psychotropics, anticonvulsants, antihistamines, ethanol and other CNS depressants. Pharmacokinetic interactions with other drugs, e.g., cimetidine, have been reported. *Drug/Laboratory Test Interactions:* No consistent pattern for a drug or test. *Carcinogenesis, Mutagenesis, Impairment of Fertility:* No carcinogenic potential or impairment of fertility in rats. *Pregnancy:* See Warnings. *Nonteratogenic Effects:* The child born of a mother on benzodiazepines may be at some risk for withdrawal symptoms and neonatal flaccidity. *Labor and Delivery:* No established use. *Nursing Mothers:* Benzodiazepines are excreted in human milk. Women on XANAX should not nurse. *Pediatric Use:* Safety and effectiveness in children below the age of 18 have not been established.

ADVERSE REACTIONS
Side effects are generally observed at the beginning of therapy and usually disappear with continued medication. In the usual patient, the most frequent side effects are likely to be an extension of the pharmacologic activity of XANAX, e.g., drowsiness or lightheadedness.

Central nervous system: Drowsiness, lightheadedness, depression, headache, confusion, insomnia, nervousness, syncope, dizziness, akathisia, and tiredness/sleepiness. *Gastrointestinal:* Dry mouth, constipation, diarrhea, nausea/vomiting, and increased salivation. *Cardiovascular:* Tachycardia/palpitations, and hypotension. *Sensory:* Blurred vision. *Musculoskeletal:* Rigidity and tremor. *Cutaneous:* Dermatitis/allergy. *Other side effects:* Nasal congestion, weight gain, and weight loss.

Withdrawal seizures have been reported upon rapid decrease or abrupt discontinuation of XANAX. (See Precautions.)

In addition, the following adverse events have been reported with the use of benzodiazepines: dystonia, irritability, concentration difficulties, anorexia, transient amnesia or memory impairment, loss of coordination, fatigue, sedation, slurred speech, jaundice, musculoskeletal weakness, pruritus, diplopia, dysarthria, changes in libido, menstrual irregularities, incontinence and urinary retention.

Paradoxical reactions such as stimulation, agitation, increased muscle spasticity, sleep disturbances, and hallucinations may occur. Should these occur, discontinue the drug.

During prolonged treatment, periodic blood counts, urinalysis, and blood chemistry analysis are advisable. Minor EEG changes, of unknown significance, have been observed.

DRUG ABUSE AND DEPENDENCE
Physical and Psychological Dependence: Withdrawal symptoms have occurred following abrupt discontinuance of benzodiazepines. Withdrawal seizures have occurred upon rapid decrease or abrupt discontinuation of therapy. In all patients, dosage should be gradually tapered under close supervision. Patients with a history of seizures or epilepsy should not be abruptly withdrawn from XANAX. Addiction-prone individuals should be under careful surveillance. *Controlled Substance Class:* XANAX is a controlled substance and has been assigned to schedule IV.

OVERDOSAGE
Manifestations include somnolence, confusion, impaired coordination, diminished reflexes and coma. No delayed reactions have been reported.

DOSAGE AND ADMINISTRATION
Dosage should be individualized.

The usual starting dose is 0.25 to 0.5 mg, t.i.d. Maximum total daily dose is 4 mg. In the elderly or debilitated, the usual starting dose is 0.25 mg, two or three times daily. Reduce dosage gradually when terminating therapy, by no more than 0.5 milligram every three days.

HOW SUPPLIED
XANAX Tablets are available as 0.25 mg, 0.5 mg, and 1 mg tablets.

Caution: Federal law prohibits dispensing without prescription. B-5-S

Upjohn THE UPJOHN COMPANY J-7384
Kalamazoo, Michigan 49001 USA February 1987

CONTINUING MEDICAL EDUCATION

(Continued from Page 415)

April 30-May 1—**Two-day Seminar on Angioscopy.** UCLA at the Neuropsychiatric Institute, Los Angeles. Sat-Sun. 14 hrs. $500. Contact: UCLA.

May 4-6—**New Perspectives in Pulmonary Rehabilitation and Smoking Cessation.** St. Helena Hospital at the Clarion Inn, Napa. Wed-Fri. 14 hrs. $150. Contact: New Perspectives Council, St. Helena Hospital, Deer Park, 94576. (707) 963-6588.

May 7—**Third Annual Cardiology Symposium.** Sutter Health at the Sacramento Inn. Sat. 6 hrs. Contact: Sutter Health CME Dept., 2020 I St., Ste. D, Sacramento, 95814. (916) 446-7681.

May 13-14—**Coronary Heart Disease: Current Concepts.** Medical Education Resources at Hilton Hotel, San Francisco. Wed-Thur. 11-13 hrs. $225-$295. Contact: MER, 5808 S. Rapp St., Suite 202, Littleton, CO 80120. (800) 421-3756.

May 19-20—**Cardiology for the Non-Cardiologist.** UCI. Thurs-Fri. Contact: UCI.

June 6-8—**Advanced Echocardiography & Doppler Ultrasound 1988.** American College of Cardiology at Sheraton Harbor Island, San Diego. Mon-Wed. Contact: Registration Secretary, EP Dept. ACC, 9111 Old Georgetown Road, Bethesda, MD 20814.

June 30-July 2—**Consultative Cardiology: Update in Diagnostic and Therapeutic Techniques.** ACC, Orange Coast Heart Institute and Hoag Memorial Hospital at Westin South Coast Plaza, Costa Mesa. Thur-Sat. Contact: Registration Secretary, EP Dept., ACC, 9111 Old Georgetown Road, Bethesda, MD 20814.

DERMATOLOGY

May 21—**Summary of Clinical Use of Argon, YAG, and CO2 Lasers for Cutaneous Lesions.** Palo Alto Medical Foundation at Palo Alto Medical Clinic. Sat. 6 hrs. Contact: Palo Alto Medical Clinic, 300 Homer Ave, Palo Alto 94301. (415) 321-4121.

August 12-14—**Dermatologic Surgery: State of the Art 1988.** Stanford University at Monterey Sheraton, Monterey. Fri-Sun. Contact: Paul H. Jacobs, MD, Dept. of Dermatology, UMC Stanford, 94305. (415) 723-6105.

August 21-28—**International Symposium: Hot Spots in Dermatology.** Kauai Medical Group at Molokai, Hawaii. One week. Contact: David Elpern, MD, 3420-B Kuhio Highway, Lihue, Hawaii 96766. (808) 245-1507.

EMERGENCY MEDICINE

May 11-15—**Tenth Annual Wound Management Workshop.** UCSD at San Diego Hilton Beach and Tennis Resort. Wed-Sun. 19 hrs. Contact: Edith S. Bookstein/WMW, PO Box 1386, La Jolla 92038. (619) 454-3212.

May 12-14—**Modern Concepts in Trauma Care Symposium.** Orange County Trauma Society at Disneyland Hotel, Anaheim. Thurs-Fri. 18 hrs. Contact: Orange County Trauma Society, (800) 368-0911.

June 6-10—**Topics in Emergency Medicine.** UCSF at Holiday Inn, Union Square, San Francisco. Mon-Fri. 32 hrs. $420. Contact: UCSF.

August 29-September 2—**Topics in Emergency Medicine.** UCSF at Holiday Inn Union Square, San Francisco. Mon-Fri. 31 hrs. $420. Contact: UCSF.

INTERNAL MEDICINE

April 16-23—**Internal Medicine.** Stanford University Medical Center at The Westin Mauna Kea, Hawaii. Sun-Fri. 25 hrs. $495. Contact: Stanford.

May 7—**Perspectives in Rheumatology.** UCLA at the Century Plaza Hotel, Century City. Sat. 6 hrs. $25. Contact: UCLA.

May 23-27—**Advances in Internal Medicine.** UCSF at Sheraton-Palace Hotel, San Francisco. Mon-Fri. 32 hrs. $440. Contact: UCSF.

May 27-29—**California Society of Internal Medicine Annual Meeting** at Nikko Hotel, San Francisco. Fri-Sun. Contact: Kathy Matikonis, California Society of Internal Medicine, PO Box 880606, San Francisco, 94188-0606. (415) 882-5198.

June 6-10—**Advances in Internal Medicine.** UCSF at Cole Hall. 32 hrs. $440. Contact: UCSF.

June 15-17—**Gastroenterology: Advances in Diagnosis and Management.** UCSF at The Mark Hopkins Hotel, San Francisco. Wed-Fri. 17 hrs. $375. Contact: UCSF.

(Continued on Page 482)

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Spare your patients the extra cost—in calories, sodium and dollars.

Spare your patients the rigors of dietary K+ supplementation.

DYAZIDE®

25 mg Hydrochlorothiazide/**50 mg** Triamterene/SKF

Effective antihypertensive* therapy...without the bananas

DAW
'DYAZIDE' AS WRITTEN.

* Not for initial therapy. See brief summary.

Before prescribing, see complete prescribing information in SK&F CO. literature or PDR. The following is a brief summary.

* **WARNING**
This drug is not indicated for initial therapy of edema or hypertension. Edema or hypertension requires therapy titrated to the individual. If this combination represents the dosage so determined, its use may be more convenient in patient management. Treatment of hypertension and edema is not static, but must be reevaluated as conditions in each patient warrant.

Contraindications: Concomitant use with other potassium-sparing agents such as spironolactone or amiloride. Further use in anuria, progressive renal or hepatic dysfunction, hyperkalemia. Pre-existing elevated serum potassium. Hypersensitivity to either component or other sulfonamide-derived drugs.
Warnings: Do not use potassium supplements, dietary or otherwise, unless hypokalemia develops or dietary intake of potassium is markedly impaired. If supplementary potassium is needed, potassium tablets should not be used. Hyperkalemia can occur, and has been associated with cardiac irregularities. It is more likely in the severely ill, with urine volume less than one liter/day, the elderly and diabetics with suspected or confirmed renal insufficiency. Periodically, serum K^+ levels should be determined. If hyperkalemia develops, substitute a thiazide alone, restrict K^+ intake. **Associated widened QRS complex or arrhythmia requires prompt additional therapy.** Thiazides cross the placental barrier and appear in cord blood. Use in pregnancy requires weighing anticipated benefits against possible hazards, including fetal or neonatal jaundice, thrombocytopenia, other adverse reactions seen in adults. Thiazides appear and triamterene may appear in breast milk. If their use is essential, the patient should stop nursing. Adequate information on use in children is not available. Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma. Possible exacerbation or activation of systemic lupus erythematosus has been reported with thiazide diuretics.
Precautions: The bioavailability of the hydrochlorothiazide component of 'Dyazide' is about 50% of the bioavailability of the single entity. Theoretically, a patient transferred from the single entities of triamterene and hydrochlorothiazide may show an increase in blood pressure or fluid retention. Similarly, it is also possible that the lesser hydrochlorothiazide bioavailability could lead to increased serum potassium levels. However, extensive clinical experience with 'Dyazide' suggests that these conditions have not been commonly observed in clinical practice. Angiotensin-converting enzyme (ACE) inhibitors can elevate serum potassium; use with caution with 'Dyazide'. Do periodic serum electrolyte determinations (particularly important in patients vomiting excessively or receiving parenteral fluids, and during concurrent use with amphotericin B or corticosteroids or corticotropin[ACTH]). Periodic BUN and serum creatinine determinations should be made, especially in the elderly, diabetics or those with suspected or confirmed renal insufficiency. Cumulative effects of the drug may develop in patients with impaired renal function. Thiazides should be used with caution in patients with impaired hepatic function. They can precipitate coma in patients with severe liver disease. Observe regularly for possible blood dyscrasias, liver damage, other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving triamterene, and leukopenia, thrombocytopenia, agranulocytosis, and aplastic and hemolytic anemia have been reported with thiazides. Thiazides may cause manifestation of latent diabetes mellitus. The effects of oral anticoagulants may be decreased when used concurrently with hydrochlorothiazide; dosage adjustments may be necessary. Clinically insignificant reductions in arterial responsiveness to norepinephrine have been reported. Thiazides have also been shown to increase the paralyzing effect of nondepolarizing muscle relaxants such as tubocurarine. Triamterene is a weak folic acid antagonist. Do periodic blood studies in cirrhotics with splenomegaly. Antihypertensive effects may be enhanced in post-sympathectomy patients. Use cautiously in surgical patients. Triamterene has been found in renal stones in association with the other usual calculus components. Therefore, 'Dyazide' should be used with caution in patients with histories of stone formation. A few occurrences of acute renal failure have been reported in patients on 'Dyazide' when treated with indomethacin. Therefore, caution is advised in administering nonsteroidal anti-inflammatory agents with 'Dyazide'. The following may occur: transient elevated BUN or creatinine or both, hyperglycemia and glycosuria (diabetic insulin requirements may be altered), hyperuricemia and gout, digitalis intoxication (in hypokalemia), decreasing alkali reserve with possible metabolic acidosis. 'Dyazide' interferes with fluorescent measurement of quinidine. Hypokalemia is uncommon with 'Dyazide', but should it develop, corrective measures should be taken such as potassium supplementation or increased dietary intake of potassium-rich foods. Corrective measures should be instituted cautiously and serum potassium levels determined. Discontinue corrective measures and 'Dyazide' should laboratory values reveal elevated serum potassium. Chloride deficit may occur as well as dilutional hyponatremia. Concurrent use with chlorpropamide may increase the risk of severe hyponatremia. Serum PBI levels may decrease without signs of thyroid disturbance. Calcium excretion is decreased by thiazides. 'Dyazide' should be withdrawn before conducting tests for parathyroid function. Thiazides may add to or potentiate the action of other antihypertensive drugs. Diuretics reduce renal clearance of lithium and increase the risk of lithium toxicity.
Adverse Reactions: Muscle cramps, weakness, dizziness, headache, dry mouth; anaphylaxis, rash, urticaria, photosensitivity, purpura, other dermatological conditions; nausea and vomiting, diarrhea, constipation, other gastrointestinal disturbances; postural hypotension (may be aggravated by alcohol, barbiturates, or narcotics). Necrotizing vasculitis, paresthesias, icterus, pancreatitis, xanthopsia and respiratory distress including pneumonitis and pulmonary edema, transient blurred vision, sialadenitis, and vertigo have occurred with thiazides alone. Triamterene has been found in renal stones in association with other usual calculus components. Rare incidents of acute interstitial nephritis have been reported. Impotence has been reported in a few patients on 'Dyazide', although a causal relationship has not been established.
Supplied: 'Dyazide' is supplied as a red and white capsule, in bottles of 1000 capsules; Single Unit Packages (unit-dose) of 100 (intended for institutional use only); in Patient-Pak™ unit-of-use bottles of 100.

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OURNAL OF THE ARIZONA MEDICAL ASSOCIATION

ARIZONA MEDICINE

APRIL 1988, VOL. XLV, NO. 4

To Do, Or Not To Do?

Marshall B. Block, M.D.

A thought permeating many editorials, both in this journal and others, is that ultimately our society is going to have to determine how much of Gross National Product (GNP) we actually want to spend for health care. With the ever spiraling costs of health care and our aging population, there are going to have to be some limits set somewhere by someone.

This is a political "hot potato" which no one person will want to field. Politicians, physicians, ethicists, economists and ultimately our citizens are going to have to decide our nation's limits. A new book entitled "Setting Limits: Medical Goals in an Aging Society" suggests that an arbitrary age limit is going to have to be set, such as 80, in which aggressive medical therapy is going to be withheld for patients who present with major medical illnesses. This is the first time a non-physician, who is labeled as a medical ethicist, has proposed such a scheme. Previously, the former governor of Colorado, Richard Lamm, suggested a similar philosophical bent when he suggested that our older population is going to have to be sacrificed for our society's general well-being. A recent article in the *Wall Street Journal* (Friday, January 22, 1988) suggests that others feel uncomfortable with this approach.

Obviously, there is opposition to such an approach by leaders of the retirement community. Furthermore, other members of the medical profession feel that there is still much waste in the medical system which, if curtailed, would provide additional funds to care for all of us without an increased expenditure in our GNP. The American Medical Association has taken a position that "the social commitment of the physician is to sustain life despite disabilities, handicaps, or advanced age" and thus physicians will have a difficult time dealing with this approach.

When patients are questioned regarding this proposal, there are obviously differences of opinion. Some patients who are elderly fear chronic medical illnesses and the need for long-term nursing care because of its cost. They are in favor of limiting medical care so that extraordinary measures are not taken just to prolong a life that has limited quality. Other patients, on the other hand, feel threatened by such a rationing approach and feel that age alone should not determine whether they should be given care. For instance, may patients in their 80's feel spry and are active. They would feel that a life-threatening illiness should be aggressively treated for they could resume their activities if they survived. On the other hand, other patients who are frail at the same age may feel that life is not worth continuing.

It is therefore difficult to set arbitrary age limits on the giving of care. It is going to be necessary for a number of points of view to be brought into focus for each individual patient in order to decide whether rationing should be undertaken. As is usually the case, when we speak about "the masses" we have consensus, but when individuals are considered, differences become very apparent. The net effect of books, such as that by Daniel Callahan, is to bring together the players who will need to make these kinds of decisions. In our current medical-legal climate, it would be impossible for us to bear this burden alone. We must draw the wisdom and expertise of others to the bedside to help us at these difficult times. ■

Marshall B. Block, M.D., Editor

JOURNAL OF THE ARIZONA MEDICAL ASSOCIATION

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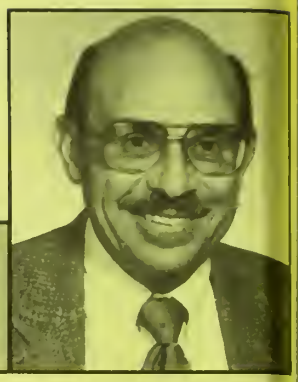

Terminal Care: Viewpoint

The following was delivered at the International Conference of Jewish Homes for Housing and Services for the Aging in Jerusalem, Israel on February 15, 1988.

Robert S. Hirsch, M.D.

A 93-year-old woman, a nursing home resident, enters the hospital with abdominal pain. It turns out that she has a marked urinary retention, and over a liter of urine is drained from her bladder by catheter. Soon her pain is relieved, but she goes on to develop pneumonia, heart failure, and acute urinary suppression. She is barely responsive. Her family is kept abreast of her condition which appears "terminal" and requests that she be "kept comfortable." Her physicians persist with treatment that is basically supportive, but involves administration of oxygen, parenteral fluid manipulations, monitoring of central venous pressure via subclavian line, antibiotics and pulmonary aerosolization. Miraculously, she begins to diurese, becomes afebrile, her chest x-rays clear and she is able to return to her nursing home residence.

The situation is an example of what the health care profession faces every day. An apparently hopeless case which turns around, a human body somehow surviving hopeless odds. Yet, there was a time during the management of this illness that physicians, nurses, and family all thought of it as "terminal," that is, occurring at or contributing to the end of life. Had the measures taken not been used, perhaps the outcome would have been less favorable. Or would death have been preferable to this exhausted nonagenerian who did not express a desire to go on with her life? We do not have laws to guide us about how and when to stop life support. We do not even have a clear idea about what constitutes life support in the most basic way and what constitutes extreme measures.

I do not want to get into a discussion of the dilemma which faces health care professionals regarding a person's right to die peacefully. Some years ago, in the Saikewicz case, the Appelate Division of the New York State Supreme Court issued a statement of the legal right of the terminally ill to refuse treatment and allow the natural process of death to run its course. These rights apply equally to the competent and non-competent. A chronically vegetative patient is, in fact, dead and life support can be abandoned. Brain dead is then the criterion. When this criterion is met, at least in New York from a legal standpoint, it would seem that there is no decision making problem in ordering a no code or do-not-resuscitate.

(Continued on page 16)

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Tail Coverage — A Concern Of All Physicians

Of grave concern to all physicians who are planning and/or anticipating leaving the practice of medicine prior to age 62 is the cost of a required double malpractice premium to provide "tail" coverage. The potential (and current) cost is staggering! The following table will give you an idea as to what you can expect. The table assumes a current $35,000 per year malpractice premium (which must be doubled for tail coverage — so we are actually looking at a current $70,000 tail premium) and projected annual rate increases of 15%, 20%, 25%, and 30%.

Years until leaving the practice of medicine	Tail premium required with projected 15% rate increase annually.	Tail premium required with projected 20% rate increase annually.	Tail premium required with projected 25% rate increase annually.	Tail premium required with projected 30% rate increase annually.
5	$140,795	$174,182	$213,623	$259,905
10	$283,189	$433,422	$651,926	$965,009
15	$569,594	$1,078,492	$1,989,520	$3,583,013
20	$1,145,658	$2,683,632	$6,071,532	$13,303,475

A question that is continually asked of MICA and this Association by our members is "Can arrangements be made to pre-pay the tail coverage, so that upon leaving medical practice, for any reason or age, the final coverage premium will be greatly reduced or eliminated?" There has not been a satisfactory answer to this question until *now*.

Through our wholly owned subsidiary, ArMA Financial Services, the Arizona Medical Association is now able to offer a **solution!** By utilizing the ArMA-sponsored Voluntary Employees Beneficiary Association, a physician or physician group can make a tax-deductible contribution that will grow tax free to provide for a "severance pay benefit". These dollars can be used to actually provide a physician with funds at the time of his/her severance from the P.C. (a taxable event) *or*, he or she may decide to direct those funds toward an offsetting deductible event — payment of the "tail" premium.

What kind of savings can this VEBA mean to you? Considerable! Let's look at the dollar figure $569,594 from the table above. (15 years until leaving practice, and across to the first column 15% rate increase.) If we assume an 8.5% return on our invested dollar and a 33% tax bracket it would take a single deposit of $241,775 15 years to grow to our projected tail premium of $569,594. On the other hand it would only take a single deposit of $161,303 ($108,073 after taxes) to the ArMA VEBA to provide that same dollar amount — $569,594. For a physician who does not have the cash flow for one-time lump sum funding it may be possible to arrange for payments over a period of years.

Unfortunately there is no mystical, magical way currently available to eliminate or even greatly reduce the actual eventual cost of malpractice tail coverage. What is available, through the ArMA VEBA, is a way in which we can significantly discount that premium through the utilization of what is sometimes referred to as the "Eighth Wonder of the World" —compound interest!

By coupling the compounding of your money on a tax deferred basis with a tax-deductible contribution, you have an excellent funding vehicle that is available only through your state medical association. ■

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ArMA Member's First Book

Everything Students Need to Know About Residencies

By Steve Nash

On January 15, 1987, **Kenneth V. Iserson, M. D.,** associate professor of surgery at the University of Arizona College of Medicine, had an idea. By December it was a book.

Getting Into a Residency: A Guide for Medical Students is the first book-length treatment of the subject. Despite its title, though, Dr. Iserson says it is a volume for any physician applying for a job.

Kenneth V. Iserson, M.D.

"There are tips on how to analyze available positions, what to wear to interviews, which questions to expect; why timing is important, how to make a comprehensible transcript report and how to get the right letters of reference — in short, basic job-getting skills from a medical perspective."

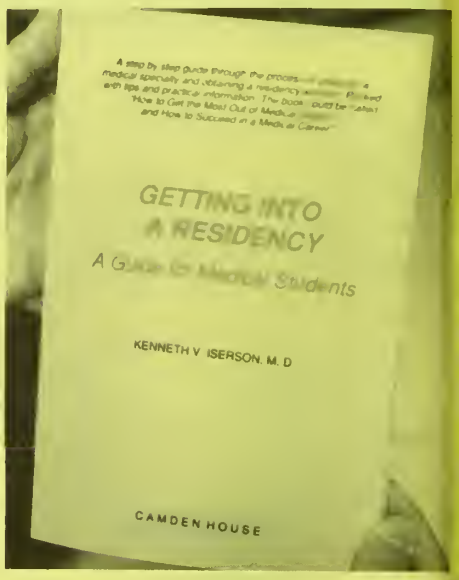
However, the book is primarily aimed at students.

"Most medical students don't begin thinking of residencies until their third or, worse, their fourth year," he says, "and that's way too late. A residency is often a life commitment. Students today, with their huge loans, can't afford to pick a wrong residency, admit the mistake, back up and go into something else. Financially it isn't possible."

To avoid this, Dr. Iserson's book recommends that first-year students investigate areas of interest. He says specialists are usually willing to let students observe or work in their offices, which allows students to see the full range of what that specialist does.

"The right residency is not as obvious as it once was," according to Iserson, who says it is no longer true that third and fourth year students get a feeling for what they like. "They only get a feeling for what practice in a university care center is like. Private practice in that specialty may not be the same at all."

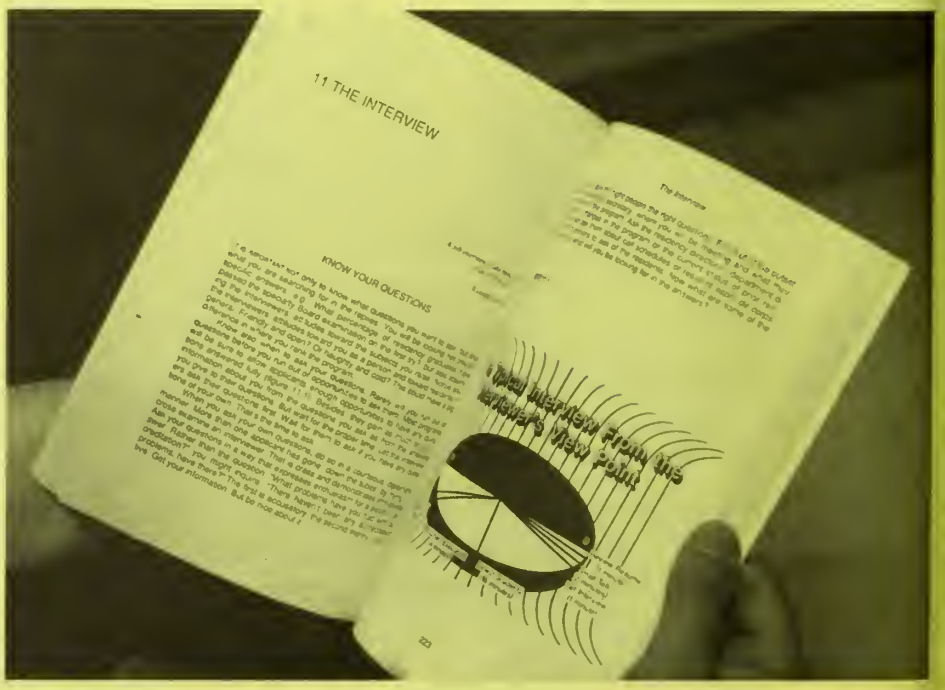
So the book urges first year students to explore the entire range



of medical practice — not just the specialty training offered by the medical school they attend — and gear their early studies in the direction they choose.

As a starting place, the book lists all recognized specialties and subspecialties, describing their scope and training requirements.

(Continued on page 18)



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Perceptions of the OIG

By Richard P. Kusserow

(Editor's note: The following is a reprint of the second half of a speech given by Richard P. Kusserow, inspector general of the U.S. Department of Health and Human Services. Mr. Kusserow presented these remarks to the annual meeting of the Federation of State Medical Boards of the United States. The first half of his remarks was reprinted last month in Arizona Medicine, along with a biography of Mr. Kusserow's distinguished and remarkable career.)

I'm going to just pass over two more quick points knowing that my time is very much limited and I would like to, if I could, respond to any questions that you all might have.

I thought it might be interesting to look at the statistics in terms of sanctions and convictions of people in the health care program, the provider side. How many of them are not physicians? And I just want to allude to them if I could for just a moment.

Less than one-fourth of the providers that are prosecuted, convicted and sanctioned are in fact medical doctors. So, when we talk about the roughly 500 people on the provider side of the Medicare-Medicaid programs that were prosecuted criminally and administratively by our office, keep in mind that we're only talking about 23 percent being physicians. Another 17 percent are other practitioners such as dentists, chiropractors and podiatrists. Seven percent provide services such as physical therapy or ambulance. Another one-fourth are suppliers such as pharmacists and neuromedical equipment suppliers. Twenty percent are health care employees other than professionals. We have only about one percent which are actually institutions, the hospitals and nursing homes. The catchall category makes up the remaining seven percent. I just want to sum up that in context for you to realize when you hear about all the sanctioning and you hear about all of the prosecutions, we're really talking about the practitioner community representing a small portion of the overall health provider picture.

The last thing I'd like to mention just briefly is some of the things that we're doing now that are coming out and that might have relevance to your work. One of the things we are continuing to do is to follow up on the studies that we have done in the medical licensure and discipline process in the United States. One of them is acting upon the witnesses we found in our own Federal programs.

In addition to being the Inspector General for roughly 35 percent of the Federal government, I'm also vice chairman of the President's Council on Integrity and Efficiency and that role carries with it the responsibility of coordinating all government wide audit and investigative activity in the Federal government. In that role, our council is focusing on physicians that are in the Federal government and how we can deal with them in terms of improving our ability to feed into your process; our ability to do our own screening in advance of employment.

We have major parts of the government that employ large numbers of physicians. Not just our department, which not only handles purchases of health services through Medicare and Medicaid, but we also have Public Health Service programs including the National Institutes of Health, ADAMAH, NIMH, CDC and the FDA. In addition to that, there is the Veterans Administration which is the largest employer of physicians. There is also the Department of Defense, and a number of other programs. Most Federal agencies, such as NASA, have on staff a lot of physicians. We're trying to see if we can government wide, put our own houses in order and make it better for you to have information plugged into your system and make sure that we use you when we're hiring employees.

In addition to that, we're doing a global study on the practice of medicine in a hospital setting. We have vested a lot in taking the stratified sample of 240 hospitals by bedsides. It's broken down into three categories, three stratifications of eight hospitals each, and we're looking at all 468 DRGs which is the basic payment under the Prospective Payment System for Medicare. We're looking at admissions, coding, treatment plans while in the hospital, and we're looking at discharge plans. We have a very rigorous study that has a three tier validation that will insure good results and give us an idea of what is actually going on in hospital settings. I will tell you that we have a tremendous amount of work going on that's looking at hospital settings. I'm far less concerned about the practice of medicine in the hospital today than I am the practice of medicine outside the hospital. I

think that individuals going to the hospitals today are getting better treatment than they ever had and I believe that there is a series of different oversight mechanisms, sentinel effects that are taking place in the hospitals that reassure me.

My concern is what happens outside of the hospital? What happens amongst those physicians that retreat from group practice, from hospital practice? And what are we doing in that area? What are we doing to be sure that individuals are getting good treatment outside the hospital? We have a number of efforts underway to see if we can find ways in which we can dig into that because I think that represents the much greater portion of the problems. Not only for you, but also for us and how we protect our beneficiaries and how to protect your patients as well as your profession. So we have a number of studies underway on this.

While I was making my circuit coming here I flew down through Atlanta to Arizona earlier this week, Wednesday I think, and in the link I stopped for messages in Atlanta enroute to Phoenix and found I had two new hearings put on, one Monday and one Thursday. The one Thursday is on PRO sanction so we're going to have that played a lot in the Congress, and that's the same committee that produced this recent legislation, Waxman's committee, of which Wyden's a member. And so we're looking at the whole PRO sanction process which we supervise. There's a lot we're doing on that side.

It's very hard for me to stay within the time boundaries. But, please let me stop at this point and perhaps I can answer some questions, if I have any time remaining.

Does anybody have any questions or anything they'd like to have me comment on that I may have slid over?

Dr. Kuiper: Don Kuiper from Michigan. Will you clearly state what kind of information you expect the PROs from the states to report to your office?

Mr. Kusserow: Well, first of all I have oversight for all of the Department of Health and Human Services programs: Medicare and Medicaid, Social Security, Public Health Service, Family Support Administration and the Office of Human Development Services.

First and foremost I'm in awe of those people and their operations. As part of that, I audit, inspect and examine not only those agencies, but the people that work with those agencies, including their contractor relationship with intermediaries, carriers and the PROs. I have total access to PRO records in terms of making sure that those programs are running properly. In fact, we're initiating a major study of the PROs. There will be 44 reports coming out, "soup to nuts," on how they're operating. I'm interested in every facet of the PRO operation. I believe in the PRO operation. Back in 1981 when PROs were being discussed, I was the only official of the administration that supported PROs.

I believe in utilization and review. I believe you must have some mechanism that can reassure the patients and the beneficiaries that they're going to receive quality health care. I believe that function cannot be performed by an Inspector General or a lay organization. It must be a professional organization. So that is a premise. I also believe as a second premise that the PROs should operate based upon outcomes and not on process. The government is so process oriented that sometimes you can't see the forest for the trees.

The whole concept basically is one that should be prospective in itself. It is in theory but it's been really handicapped by a lot of compromise with the Congress. There's kind of an askewed program that comes about as a result of these compromises. So we're looking at the PROs as to what problems you're encountering and what it is that can make them run better.

I think your question is more directed towards the sanctions process. There are about 12 steps in the PRO sanction process and it goes back to the old PSRO program and its failure which was generally recognized. The two grounds that were most often cited for its failure were the inability to sanction and the fact that they never had to verify instructions. They never had the brakes come out with the PROs, the brakes come out and they have the ability to propose sanctions. But they're a little worried about that because they want to be sure it's consistent and meets both the medical and legal sufficiency test. Therefore, we were built into the process.

Basically, when the PROs encounter something in a hospital practice which is questionable, whether it be over utilization or practice, the primary means for its resolution should be through dialogue. It's only when the problem is gross and flagrant and imperils the patient or where the practitioner refuses to cooperate with the process that they would recommend a sanction. If a sanction is recommended, then it comes to us at the same time it goes to the physician. We then review for both medical and legal sufficiency.

(Continued on page 13)

Admissions Criteria For Entry To Medical School

On the first day of orientation for each incoming medical school class, the Dean welcomes the new class and, among other things, describes some of the interesting and unique features of their class to them. For example, for the class entering in August, 1987, although all the students were Arizona residents, they came from 21 schools in other states ranging from the East to the West Coast as well as the three Arizona universities. Ages of the class members ranged from 19 to 39. Although the majority had undergraduate majors in the traditional areas of biology, zoology, biochemistry, chemistry and microbiology, the class also included students with majors in animal science, anthropology, astronomy, bioengineering, civil engineering, computer science, dance, electrical engineering, English, finance, general studies, health education, math, medical technology, nursing, nutrition, pharmacy, philosophy, physics, physiology, psychobiology, psychology and sociology.

What we hope is clear from the above is that the criteria used for selecting students for the University of Arizona College of Medicine do not restrict the variety of backgrounds or the breadth of training areas that applicants may present for consideration by the Admissions Committee.

There are five major areas which are reviewed in the selection of each medical student:

1. *The Academic Record*. The Admissions Committee looks at all aspects of the academic record. Although some portions of the record will be more important than others for a particular individual, included is the undergraduate course record and GPA, graduate courses, semester course loads, trends in grades from college entrance to the present, credit hours in science and other areas, and the breadth and range of courses taken. Also looked at is the amount of time spent in extracurricular activities, the number of hours worked per week, and volunteer work or other activities. All of these help in understanding what the student's total academic life is like and how the time has been spent. Note that nothing has been mentioned about particular majors. Everyone applying must take the required science and English prerequisite courses but beyond that no particular major carries more weight than another. In fact, in the interest of assembling a class that includes people with different skills, interests and abilities, students are encouraged to major in an area in which they are interested and not base their choice on what they believe might be attractive to a medical school.

2. *MCAT Scores*. The Committee looks at the score obtained on each MCAT subtest, the scores for each time the MCAT was taken and the trend or improvement in scores. The scores are also compared with performance in the relevant courses.

3. *Interviews*. All Arizona applicants and some applicants from three WICHE states without a medical school (Alaska, Montana and Wyoming) are invited for interviews. Each applicant is interviewed by three College of Medicine faculty interviewers and a fourth interview is conducted, at a different itme, with a physician in practice. The interviewers are asked to focus on the applicant's personal characteristics rather than the academic record and are given no advance information. Interviewers are asked to assess the applicant's interest in medicine as a career, and interest and participation in outside activities during the school years. Interviewers will also assess other characteristics including flexibility, maturity, motivation, and verbal skills and expression. The reports submitted by the interviewers are an important and often critical part of the assessment of each applicant.

4. *Pre-health Professions Committee Recommendation or Letters of Recommendation*. The Admissions Committee's preference is for the use of a Pre-health Professions Committee recommendation, accompanied by additional letters if necessary. The Admissions Committee takes seriously the letter

(Continued on page 18)

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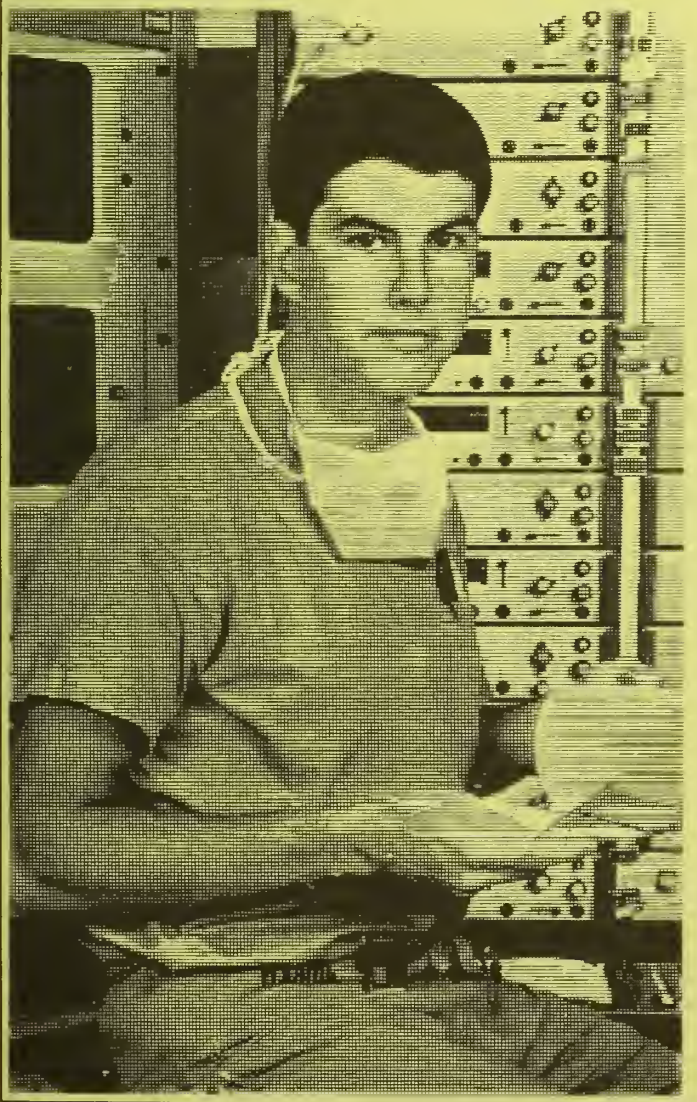

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Universal Infection Precautions Enter Mainstream

Universal Infection Precautions (UIP) are gradually being introduced into the medical mainstream, both in the doctor's office and in the hospital.

Nationally and in Arizona, more and more hospitals are taking steps to educate employees on the various aspects of UIP. Recently, Humana Hospital-Desert Valley conducted an in-service training program on UIP for both Humana employees and infection control specialists from a number of other Valley hospitals, followed by a presentation at the regular medical staff meeting.

Participants included local physicians, epidemiologists, infection control specialists and a national authority on infection control and preventive practices, Marguerite Jackson, RN, MS, CIC, director of the epidemiology unit, University of California-San Diego Medical Center.

Following are some of the key questions discussed during the programs, together with composite answers.

Q. What are Universal Infection Precautions?

A. The objective of UIP is to prevent disease transmission and protect patients as well as health care providers by treating all body substances of every patient as potentially infectious regardless of the patients' diagnosis.

Q. What is the status of UIP within hospitals?

A. In August, 1987, the National Centers for Disease Control published recommendations for UIP, with the emphasis on prevention of disease transmission for patients and workers. More recently, the federal Department of Labor's Occupational Safety and Health Administration (OSHA), has begun the process of possibly developing a program of enforcement to ensure that health care employers are implementing appropriate measures to protect health care workers. In November, OSHA requested input from hospitals and other healthcare agencies all over the country on proposed rule-making. Other organizations such as the American Hospital Association are also advocating the practice of universal precautions.

Q. What makes UIP different from the usual precautions traditionally seen in hospitals?

A. The major change in concept is that instead of waiting until a diagnosis is made on a patient and then isolating him, hospitals will consider all patients' blood and body fluids as potentially infectious. UIP is not based on the patient's diagnosis but rather it is an interaction-related approach. Thus, this will be a prospective rather than retrospective approach.

Q. What are some examples of UIP?

A. The main procedures we will see are:

1) Hypodermic needles will not be recapped and will be disposed of in puncture-resistant containers placed in each patient room and other points of use.

2) Gloves will be worn when coming in contact with any body fluid, including blood, urine, feces, mucous membranes and open wounds.

3) Handwashing after contact with blood or body fluids, even when gloves are worn.

4) Gowns, masks and goggles will be worn in situations where health care workers risk having eyes, mucous membranes, non-intact skin or clothing splashed or soiled by body fluids.

5) Soiled linen will be placed in leak-resistant bags.

6) Trash and infectious wastes will be disposed of according to city codes.

7) The traditional signs (usually on patient door) used for infectious processes will no longer be utilized.

8) Respiratory/airborne diseases will be addressed individually by each hospital — some will utilize a "stop-sign" or "alert" system. Basically, these patients will require a private room, and masks will be worn by the health care provider.

Q. Will the elimination of isolation signs pose problems?

A. It should not, but it is one of the significant changes. Actually, it should enhance consistency in the practice of precautions being applied to all patients, not just those with a "sign on the door." The objective is to treat all patients' blood and body fluids as potentially infectious. Since patients will be treated the same, no signs are needed. Under the new UIP system, each health care provider entering the patient room will have been educated to take the proper precautions based on the procedures, and the risk of contact with blood or body fluids they will encounter.

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Perceptions

(Continued from page 9)

What we look for in these sanctions is the fact that they have stated a case that would first warrant the sanction and second, the sanction that they're proposing is supportable. What we have found is that practitioners are harder on themselves than lay organizations. In some cases, PROs may take a very hard line and have a very dim view of practices that have been presented before an outside review by somebody who is not a physician.

So we've looked through the 30 million discharges that we've had since the advent of the prospective payment system, there have been 6,500 cases targeted by the PROs, with only 104 of the submitted cases recommending sanctions. Of that number, only 39 resulted in a sanction of a physician. Most of these cases resulted in deaths that were unnecessary. The balance were practices where the physician refused to modify behavior. Therefore, the PRO felt constrained to have no other choice but the sanction. My concern is not that they've been too aggressive, but that on balance the PROs have not been aggressive enough. It's very uneven as to where the sanctions are coming from and we still have a very large number of states that have not submitted one recommendation for sanction, even when we had evidence to show that there were problems with certain individuals and hospitals. What we look for is that you make a clear case. One that meets medical sufficiency and that what is being alleged is in fact correct. That the severity of its consequence is correct and it meets the legal needs. Once it's done that, then we will do one of four things. We have four choices under the law. One is to do nothing and in 120 days that sanction goes into effect. The second is to reject it. The third is to accept it as it is, and the fourth is to mitigate it, except mitigate it by striking out counts for mitigating the penalty.

The statistics are that only 39 of that 104 have resulted in sanctions. We've had 15 that we've rejected out of hand, most have been mitigated and some have been dropped because somebody's withdrawn from medicine or somebody has withdrawn from the mortal plain. So there aren't that many cases in the process. Again, we look for medical and legal sufficiencies. We have a medical staff that reviews the medical side and we have a legal staff that reviews the legal side.

Question from the audience: Regarding the clearinghouse, the information is to essentially be confidential except for certain groups. Is your office, the Medicare and Medicaid office going to receive the information from the clearinghouse?

Mr. Kusserow: I have access to everything in the department, predecisional and otherwise. I have access to anything outside of our office or outside the department when it deals with our department's programs. In fact, I've been granted subpoena power, enforceable by the United States District Court. That includes the patient records that have been reviewed by PROs. I'm an exception. So, yes, I will be an exception. If I have a need, I can go into those records.

My great concern about the clearinghouse is again the construction. It is designed for one purpose and that purpose should be followed. There's a tendency sometimes to take a data bank and do more with it than originally intended. I don't think there's any way you can resist that. That information should be protected and limited to exactly what was intended by the Congress and not go beyond that, and I will work to make sure they will adhere to that. Some of the information is certainly damaging and it really doesn't provide a whole lot of information. I'm sure that it's limited to the old concept of "need to know" and that's what we're working for.

Question from the audience: Another question about the clearinghouse. Would you elaborate on the internal advisory board's discussions about including other practitioners and what implication, if any, that will have for designation of a contracting organization?

Mr. Kusserow: H.R. 1444 is the bill that has not yet passed but which represents a pattern that resulted in the Wyden bill coming through. Actually it sets forth that there will be allied professions included, not just medical practitioners. The Wyden bill left it dangling. It said that it will be the medical profession and basically leaves it up in the air if any others should be included. It leaves the door open. Now we're confronted with an open door and no mandate to include other types of health professionals. We have another bill that would mandate it and which is looking very promising to pass. The question is how do you go about straddling it?

I can tell you that up until a few weeks ago what the advisory committee did not understand is the type of data elements that you have and how you operate. It is different than what you have with undertakers and other types of people being licensed in the states. It's a different system. Undertakers, and in some states the florists, plumbers, chiropractors, podiatrist and pharmacists go through a Department of Education and Registration that is dif-

ferent. It is an entirely different system that's operating and quite frankly it operates on a much more primitive scale than what you're doing.

How do you meld those two dissimilar systems? I don't know. The closest thing that you could have now is dentists. But if you start adding these others just to be operated by a single clearinghouse, that would have an effect. And how the RFP is developed is under debate right now. Should we start off having numerous different clearinghouses or should we have an umbrella clearinghouse that would take care of anything that may come down the road. This is a major debate point right now — how should we go about doing it? The decision has not been made final as to which way we're going to go.

I think that one of the things we're doing is to study these other professions. How they handle licensure and discipline and how they track it and everything else, to have a better understanding as to what it would take to meld the two if that is the way this is going to go. That's a major issue right now. That's probably the major issue up in the air as to how you go about casting the RFP.

Question from the audience: Will you comment briefly on the PRO due process and the sanctioning or lack of due process in the PRO sanctioning process? There's been concern expressed.

Mr. Kusserow: For the people who couldn't hear in the back, the question really relates to whether I commented on due process or lack thereof in the PRO process. There is a lot of due process. In fact, there's more due process in the PRO sanction's area than almost any other sanctions processed in the Federal government today. The concern is where do you put it. Now, under the law it's very carefully constructed because of the experience of the PSRO. They wanted to balance it.

Let me just recount some of the steps that are involved. One is that it's supposed to be a collegial process in the hospital. The purpose is that the PROs should work with physicians that may not have kept pace with rising biomedical research and the benefits thereto. Or, that they may have slipped in some way in the practice of medicine with the idea of trying to correct it. Sanctioning comes in when you fail or where it's incorrectable. So you have two tracks that are followed.

First is the area of gross and flagrant practice where patients are imperiled and it's not by mistake. The second area is where there's a pattern of practice and the physician refuses or is unable to correct this pattern. But in both, the first step is the encounter. They invite the physician in and discuss it. They bring whatever information they have and see if it can be resolved, and in most cases they have been able to resolve the identified problems through this process where no sanctions have resulted. So, it does work.

When the PRO proposes a sanction, they send out a proposal letter. The exact same letter that comes to our office goes to the physician. The physician then has 30 days in which to respond. It is almost like responding to a bill of particulars. During that period of time we only review to see if all the paperwork is correct. If not, we reject it. But, if the paperwork is correct, we then wait for the physician's response. Once received, the regional office sends it to Baltimore where it undergoes two reviews. One is the medical sufficiency review and one is the legal sufficiency review, and then one of the four steps that I previously mentioned takes effect.

Let's say if it goes through to a sanction, the physician has a right to appeal for a de novo hearing on the facts with the administrative law judge and he has an adversarial judge and counsel and they can litigate. If they're dissatisfied with that outcome, they can appeal to the department. If they're not satisfied with that, they can then appeal to the courts. So there's a lot of due process.

The question that has come up is how many due processes should there be to this so-called collegial setting where physicians are sitting among themselves? In the early days, we had some cases where the PROs didn't have transcripts. They took notes, and there was some question as to whether that was really a fair process. And the current court cases relate to these early sanctions. This doesn't happen anymore.

The questions being asked are: Should a physician have the right to counsel? Well, that's an error in the Constitution. Should they have a right to counsel? That seems reasonable, doesn't it? You can have counsel there advising them. But, should that counsel be able to bring in witnesses? Expert witnesses that could corroborate that the treatment plan that's in question was, in fact, correct? You can say that doesn't seem unfair. That would be fair. If they have that, then you can have witnesses and evidence. Can the attorney representing the physician ask a question for clarification? Is that unreasonable? Can they ask a PRO a question? That doesn't seem unreasonable. What you get though, somewhere along the line, is the de novo hearing on the factual evidence. If that's the case, I don't care one way or the other. If you want to have the hearing in the hospital and if Con-

gress wants to have that hearing in the hospital, it helps me. I don't have to go through all that process. But, then they shouldn't have the second one. My point is that there should be only one hearing on the facts.

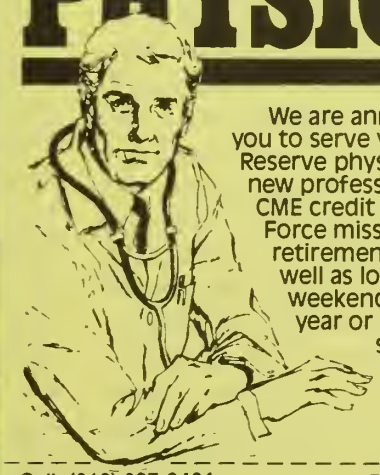
If you go with having the hearing prior to a sanction and then the administrative law hearing process, I'm here to tell you that the physician community may, in fact, be harder than would a layman that's hearing the same evidence at the first hearing. If you move the process more into the hospital, you have problems. Plus the fact that once you put attorneys questioning in the process you have a different character to a hearing.

And that's the whole issue of due process. The whole idea of a gross and flagrant violation is that if you have somebody that is harming patients because they're drug impaired, alcohol impaired, disease impaired, age impaired, you want to get them out. We don't kick them out of medicine. That's your job. Our position is that we shouldn't have beneficiaries getting second class medicine. Our prime concern is the patient. And, our department is paying for first class medicine.

They're reluctant participants now. They should realize that if they are harming the patient, that we should move quickly to get them out and have the full adversarial hearings and the due process which may take many, many, many months. In a period of time they're out. If they want to appeal it and come back in on that by added due processes and hearing, that's fine, but we want to protect the patients during that period of time. I think it would be disastrous if there was not a mechanism to remove a physician who was harming patients.

I don't think in the final analysis that the courts or the Congress could accept that. So that's at risk now.

PHYSICIANS



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A GREAT WAY TO SERVE

Terminal Care

(Continued from page 2)

Brain vs. Soul

Byrne in the November 2, 1979, issue of *Journal of the American Medical Association* wrote an article entitled "Brain Death: An Opposing Viewpoint." In this article he stressed that cessation of total brain function, whether irreversible or not, is not necessarily linked to the death of the person. The concept of brain death reduces the life of the person to a function of the material brain. Brain function then takes the place of the immaterial principle or "soul" of man. This philosophical option is in contradiction to the religious beliefs of Christians, Jews, Moslems, Hindus and many others. Thus, a moral and philosophical dilemma can appear from an apparently clear cut situation. Can we here substitute the phrase "end of useful life" for brain death? This is not the only type of circumstance which defies answer.

Conflicting Views

Much more frequently, the situation is one of bursting activity, stress and anguish. A patient who has been in good health suddenly hangs by a thread and is kept alive by tubes, complex machines, and the heroic efforts of attending personnel. The patient hasn't given thought during his healthy days to writing a Living Will for himself, so his wishes are not known. The family members are distraught and cannot begin to cope with the life and death decisions which must be made —how far and how long should this all continue? The medical and nursing people all the while are persisting with what they have been trained to do best —preserving and prolonging the life. Enter then the pastoral services, social services, psychologists and thanatologists and we soon have a monstrous disparity. Those who view things philosophically will argue for the death with dignity of the patient. Those who are imbued with the technical knowledge and capability to sustain breathing, heart pumping, fluid balance, and to control hemorrhage, fever, shock and so on down the course can see a glimmer of hope even in the most hopeless situation.

Seeking Answers

Do physicians draw upon the classical roots of the profession to find the idea of an obligation to prolong life? Interestingly, no. In a report to the Hastings Center Research Group on death and dying, Darrel Anumdsen points to the Hippocratic aphorism that the ideal for the physician was to help, or at least to do no harm. In classical Greece and Rome, if a physician based his decision to undertake a case only on the consideration that the treatment he have would simply prolong the life of a patient for whom there was no hope of recovery, he would be completely free to refuse. In fact, in the Hippocratic writings, one role of medicine was to refuse to treat those who are overmastered by their diseases, realizing that in such cases medicine is powerless. The feeling was that if treatment would simply prolong life, the patient's interests would not be served. Indeed, this might be viewed as harming rather than helping the patient. On the other hand, a frequently articulated concern among physicians was the possible damage of such unsuccessfully managed cases to their reputations, a more mundane consideration, to say the least. The physician Celsus said "It is the part of a prudent man first not to touch a case he cannot save and not to risk the appearance of having killed one whose lot is but to die." And Amundsen quotes Danielle Goureviteh as saying of the Greco Roman physician "he would feel guilty if he undertook a cure he could not successfully carry out."

Those days of antiquity were simpler — no professional licenses, no laws mandating professional behavior and certainly very little capability for reversing nature's inexorability.

Death: Not Inevitable

And that is the problem. I think that our society feels that death is not inevitable. What appears to be terminal, the end, can, with enough technology and expertise, be pushed back to pre-terminal and even well-being. For all the thinking on death and dying, on dignity, caring, ethics and humanity, the triad — the health care professionals, the patient, and the family all have different needs to be reconciled. Therefore, we must continue to grope and cope, to employ all the technology, art, and wisdom we can muster to prolong life until someone else makes a decision. We can prognosticate and recommend, but in the final analysis, must be told what to do.

The question then remains about whether guidelines for the behavior of health care professionals in "terminal care" situations will be forthcoming.

Traditional Care

In his book, "Hospice — A Caring Community," Dr. Ted Koff maintains that generally available traditional care is often inhumane in that it prolongs suffering, extending physical life with total disregard for the quality of life. It ignores or transgresses the dignity of the individual and inflicts unnecessary isolation of the patient from family, home and friends, at a time when they are most needed. And traditional care is often unsuccessful in controlling pain, and it can be exhorbi-

tantly expensive. I can't quarrel with any of this, but as a physician, I don't have a clear idea of when I should start or stop the support for these patients, and I and my colleagues face this quandary daily.

Let's face it — living is a terminal condition. A newborn deprived of food and fluid is as sure to die as an end stage cancer patient deprived of the same. Another Hastings Center report by Lynn & Childress published in 1983, addresses the question, "Must patients always be given food and water?" The topic is examined closely and at length, reviewing all the methods of hydration and nutrition and the many different types of cases under which they might be employed as, for example, in Down's Syndrome babies.

Limited Conclusion

A limited conclusion is reached. "Our conclusion that patients or their surrogates in close collaboration with their physicians and other caregivers and with careful assessment of the relevant information, can correctly decide to forego the provision of medical treatments intended to correct malnutrition and dehydration in some circumstances is quite limited." Is this basic decision to be made before or after other support measures are initiated? My question! Lynn & Childress also point out that in most cases incompetent patients are best served by receiving nutrition and hydration, because such patients may often expect long life and would suffer anguish if not fed or hydrated. From the tone of the article, it seems to me that the authors agonized over its content and conclusions. But the conclusions are, as is usual in writings on this subject, amorphous and provide us no usable guidelines. Nor are the many other papers that I have read on the subject more helpful.

Legal Guidelines

Are courts or legislatures providing clear guidelines? With the possible exception of New York's Saikewicz mentioned before, states have no clear laws addressing this issue. On the other hand, a New Jersey appellate court recently affirmed that a hospital had to follow the wishes of an amyotrophic lateral sclerosis victim to have her feeding tube removed, thereby allowing her to exercise her right to die. The hospital which had a strong institutional policy against withholding food and fluids from patients had lost the decision in trial court, and then entered the appeal. Is this to be a precedent, and if so, what range of situations can it cover? We shall see.

And then there are the wishes of the patient to be considered. Is dying dignified? What is the bond to life? Is possible afterlife or other reward a balancer? Is Simone de Beauvoir correct when she says "Whether you think of it as heavenly or earthly, if you love life, immortality is no consolation for death." And Bertrand Russell says that if a person survives death, the memories and habits which constitute the person will continue into a new set of occurrences. If the brain as a structure is dissolved at death, this is impossible. These philosophical statements which fill many volumes on the subject of death make interesting reading, but shed no solace on our dilemma of terminal care.

Dealing with Dying

I will quote a study in a New Nursing Skillbook called "Dealing with Death and Dying." 174 nurses were queried. 84% said they would support a terminally ill patient's request that life sustaining measures be withheld. 94% said that the patient's desires should take priority over those of relatives or spouses. And one nurse added that it almost seems against the law to die in peace. As Ruth Gray, R.N. has said, "We need to come to accept and understand the fact that dying is as much a part of life as birth." Unfortunately, for now, our society does not fully accept this. Therefore, the unease of the health care professions in dealing with terminal illness will persist.

The poets and philosophers may fret about the subject of death. John Dryden writes that —

"Ev'ry man who lives is born to die.

Like Pilgrims to th' appointed Place we tend, The World's an Inn, and Death the journey's end."

Or Alexander Pope —

"Oh let me live my own, and die so too! (To live and die is all I have to do.)."

They all see the inevitability. But Yiddish proverb casts it in a somewhat different light.

"Ever since dying came into fashion, life hasn't been safe."

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Admissions Criteria

(Continued from page 10)

provided by the Pre-health Professions Committee for several reasons, including the fact that typically this committee will have had more extensive contact with an applicant than will the medical school interviewers and can therefore provide information based on contacts with the applicant over a period of time. An evaluation of medically-related activity (volunteer or otherwise) which the applicant has been involved with is also helpful to the Committee.

5. *Personal statement.* The applicant's one page personal statement is reviewed by all Committee members. The statement gives the Committee a glimpse of what is important to the applicant and can often be helpful in understanding unique characteristics that may not be clear in any of the other material in the file.

It is important to note that the Admissions Committee is committed to absolutely fair and equitable treatment for all applicants throughout the review and selection process. All of the applicants to be considered are reviewed by the Admissions Committee. The names of those selected are then submitted to the Dean who sends the acceptance letters.

Many physicians from Flagstaff, Phoenix and Tucson participate by volunteering to interview a small number of applicants each year. The interviews are a critically important part of the process and we appreciate the help from physicians in Arizona. If anyone not previously contacted wishes to be included in the interviewing process or if there are questions about any aspect of the process, please feel free to call the College of Medicine Admissions Office.

Shirley Nickols Fahey, Ph.D.
Associate Dean
Vincent A. Fulginiti, M.D.
Acting Dean

Universal Infection Precautions

(Continued from page 12)

Q. Who will these procedures affect most?

A. All groups — patients, health care workers and physicians — will be better educated and protected. All patients will be treated the same, whether colonized, infected or non-infected.Thus cross-transmission from *all* patients should be interrupted and reduce infection risk and provide broader protection. UIP will also protect physicians and employees from infectious diseases such as Hepatitis B, a far more profound risk than acquired immune deficiency syndrome.

Q. How will these practices be introduced into hospitals?

A. The introduction of these procedures will involve major changes in attitudes, knowledge and behavior of all health care providers. Extensive education programs will be required of all personnel—from housekeeping to nurses and physicians. Administrative and medical staff support is key to implementing the changes needed. Each hospital will develop its own policies. From the planning stage to implementation may require up to a year or two, depending upon the hospital's size.

Everything Students Need to Know

(Continued from page 6)

The number of programs offered with the number of positions open is given in approximate figures, and the programs are rated by difficulty to enter.

Applicants to residency programs will find the second half of the *Getting Into a Residency* a trove of technical information on anything from where to find matching forms to practical tips for interviews and analyzing programs. There is a bibliography and detailed index, prepared by Dr. Iserson himself, designed to aid the thorough student.

Dr. Iserson is uniquely qualified to give such advice. As residency director for emergency medicine at the College of Medicine, he receives over 400 applications for the six available spots each year. In addition, he has been an active student advisor since the late 1970s. His undergraduate degree was in education, and his business and analysis skills were sharpened as he earned his M.B.A.

He says writing a book so quickly was like having a full-time other job, taking a lot of nights and weekends. His wife, Mary Lou, a certified public accountant, did the editing and was the "resident computer expert."

"The book reflects my thoughts, but is research-based," Dr. Iserson said, adding that he also drew on the feedback from

(Continued on page 20)

New Active Members

The Arizona Medical Association welcomes the following new members:

COCONINO

Holly K. Vigil, M.D.
Obstetrics & Gynecology
1300 North Rim Drive, Flagstaff
University of Colorado
School of Medicine - 1979

MARICOPA

John M. Lewis, M.D.
Ophthalmology
4760 Falcon Drive, Mesa
Washington University
School of Medicine - 1982

Steven J. Englendar, M.D.
Public Health, Pediatrics
3008 North 3rd Street, Phoenix
Case Western Reserve University
School of Medicine - 1973

Zachary B. Gerbarg, M.D.
Internal Medicine
13041 North Del Webb Boulevard
Sun City
Albany Medical College-
Union University - 1979

David W. Tellez, M.D.
Pediatrics, Critical Care Medicine
1111 East McDowell Road, Phoenix
University of California
San Diego School of Medicine - 1981

YUMA

Abdul S. Lalani, M.D.
Otorhinolaryngology
2189 South Avenue A, Yuma
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(Continued from page 18)

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Dr. Iserson earned his M.D. from the University of Maryland, Baltimore, in 1975. He did a straight surgery internship at the Mayo Clinic, and an emergency medicine residency at Cincinnati General Hospital from 1976 to 1978. He is board certified in emergency medicine.

Dr. Iserson is a fellow of the American College of Emergency Physicians and is a member of the American Medical Association, the Arizona Medical Association and the Pima County Medical Society. ■

Talking To Comatose Patients

Physicians don't spend much time talking to comatose patients, but a report in the *Archives of Neurology* suggests they should. John La Puma, M.D., now of Lutheran General Hospital, Park Ridge, Illinois, and colleagues at the University of Chicago Hospitals and Clinics, Chicago, say doctors may not speak to comatose patients for various reasons: because they don't seem to hear or respond; because speaking won't affect their clinical outcome; and because time spent with them takes time away from other, more "viable" patients. Research indicates, however, that comatose patients may indeed be able to hear, the authors say. What's more, "not talking to comatose patients may promote the notion that they are dead or nearly dead; not talking may become a self-fulfilling prophecy, influencing physicians to inappropriately withhold or withdraw therapy," they say. "We should talk to comatose patients because they may hear, because some comatose patients get better, and because we are caring professionals."

Fiber Supplement May Lower Cholesterol

A report in February's Archives of Internal Medicine says an over-the-counter dietary fiber supplement may be as effective a cholesterol-lowering agent as some often-prescribed drugs. The study, by James W. Anderson, M.D., of the University of Kentucky, Lexington, and colleagues, involves psyllium hydrophilic mucilloid, a natural, soluble fiber derived from the seed husks, by 26 men with mild to moderately elevated serum cholesterol levels (188 to 314 mg/dL). After eight weeks, the double-blind, placebo-controlled study found psyllium use lowered total serum cholesterol levels by 14.8 percent and cut levels of low-density lipoprotein by 20 percent. Psyllium treatment did not affect body weight, blood pressure or serum high-density lipoprotein levels. "Subject adherence to psyllium treatment was excellent, and no adverse effects were observed," say the authors of the study, supported by G.D. Searle & Co., Skokie, Illinois, and the Proctor & Gamble Company, Cincinnati.

Causes Of Death In Term Newborns

Most studies of newborn mortality focus on premature infants, who most often die of respiratory problems. But a different spectrum of disease and causes of death are seen among full-term infants, a study in February's *Archives of Pathology and Laboratory Medicine* says. The report, by Nancy Rosenthal, M.D., and Carlos R. Abramowsky, M.D., of Case Western Reserve University and University Hospitals of Cleveland, also notes changing trends in mortality among term newborns since World War II. Major congenital abnormalities were the main cause of death in 59 percent of the 342 infants Rosenthal and Abramowsky studied, compared with 28 percent noted in a 1970 study and 18 percent in a 1953 report. Perinatal injury and perinatal placental problems accounted for 53 percent of newborn deaths in the 1953 study, versus 20 percent in the new report. "With improvements in the management of high-risk pregnancies and infection, these problems have been significantly reduced, so that if a term infant dies today, it is most likely due to a congenital anomaly incompatible with life," the authors say.

Zipper Access To Abdominal Infection

Although draining necrotic or infected tissue in patients with severe abdominal sepsis is key to patient survival, repeatedly getting into the abdominal cavity to accomplish this can be difficult. But authors writing in a recent *Archives of Surgery* say a nylon/polyethylene zipper or zipper/mesh combination can provide easy abdominal access until treatment

of the infected tissue is complete. J.L. Garcia-Sabrido, M.D., Ph.D., of the Hospital Provincial, Madrid, and colleagues, report using the zipper technique since 1982 to treat 49 patients with necrotic pancreatitis and 15 patients with severe intra-abdominal sepsis due to intestinal perforations. Mortality in both groups was sharply lower than expected. "We attribute this decrease to the open-abdomen technique that allowed for daily abdominal laparotomies to completely evacuate septic foci in the abdomen," the authors conclude.

Protecting Against Accidental Eyedrop Misuse

Topical eye drugs, especially when used improperly, may cause not only eye injuries but systemic problems as well. A letter in the *Archives of Ophthalmology,* noting that many ophthalmology patients often are prescribed multiple eye medications, notes the potential for misuse of these drugs by patients who inadvertently mix up the caps between different bottles. "We have noted numerous situations where bottles and caps are mismatched, especially in our elderly patients with glaucoma who have advanced optic nerve damage and use as many as three types of topical eye drugs routinely, and often five types in the early postoperative period when they are further incapacitated," write Ronald E.P. Frenkel, M.D., of Detroit, and colleagues. Color-coordinating caps and bottles might help protect against such accidents, the letter says. "An additional possibility would be to have varying threading sizes of the caps so that each colored cap could only screw onto the identically colored bottle," they suggest.

Oral Zinc In Macular Degeneration

Oral use of zinc may slow the age-related macular degeneration (deterioration of the central part of the retina) that is a major cause of severe visual loss in the elderly, says a report in a recent *Archives of Ophthalmology.* Authors David A. Newsome, M.D., of the Louisiana State Medical Center School of Medicine, New Orleans, and colleagues caution that the pilot nature of their study and potential complications of oral zinc use mean "widespread use of zinc in macular degeneration is not now warranted." Still, they note, the double-blind, placebo-controlled study of 151 patients with macular degeneration showed zinc-treated subjects had significantly less visual loss than the placebo group after 12 to 24 months follow-up. "This is the first controlled oral intervention study to show a positive, if limited, treatment effect in macular degeneration, a major public health problem," they find.

Racial and Familial Factors in Otitis Media

Racial factors seem to play an important role in the middle ear inflammation otitis media, a report in a recent *Archives of Otolaryngology-Head and Neck Surgery* says. Marco V. Goycoolea, M.D., Ph.D., of the Minnesota Ear, Head and Neck Clinic, Minneapolis, and colleagues studied 220 children aged 5 to 9 years who live on Easter Island in the Pacific. This was an ideal population for evaluating racial factors since it included three groups of children who differ only in racial and familial background—natives, children of mixed parentage, and "continentals" (birth origin other than on the island). The authors found no otitis media cases among the genetically pure natives, 10 percent prevalence among children of mixed parentage, and 11 percent among the continentals. This suggests "the presence of intrinsic or pronicity (tendency) factors that are seemingly transmissible," the study concludes.

Serum Iron In Adolescent Alcohol Use

Alcohol use alters adult iron metabolism, predisposing to excess iron storage in the liver and possibly liver damage. Now, a study in a recent *American Journal of Diseases of Children, AJDC,* says adolescent alcohol users have elevated serum iron concentrations that increase incrementally with drinking frequency. Authors Ira M. Friedman, M.D., now of the University of California, Berkeley, and colleagues looked at drinking frequency and iron metabolism in 591 male and 614 female teenagers who took part in a national health survey in the 1970s. Alcohol had greater effects on iron metabolism in males than females; transferrin (an iron-transporting protein) saturation and hemoglobin concentration in the males paralleled their alcohol use. "These abnormalities may be precursors of hepatic iron overload and chronic liver damage," the authors conclude, saying more long-term research is needed.

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Allergic Contact Dermatitis Involving Gold

Gold is an inert, insoluble metal, and allergic contact dermatitis (ACD—skin inflammation) resulting from gold jewelry or dental implants is rare. But a letter in a recent *Archives of Dermatology* describes two patients seen less than six months apart with apparent ACD linked to gold jewelry. Joseph F. Fowler, Jr., M.D., of the University of Louisville Kentucky School of Medicine says physicians should be aware of this problem, which seems more common in women than

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Clinical Investigation

Immunoresponsiveness in Ulcerative Colitis and Crohn's Disease—Effect of Colectomy and Suppression of Disease Activity

JOHN LYANGA, MD; PAUL DAVIS, MD; *and* ALAN B. R. THOMSON, MD, PhD, FRCP(C), *Edmonton, Alberta*

We evaluated the effect of medically induced symptomatic disease improvement on in vitro tests of cell-mediated immune responses in 33 patients with Crohn's disease. When results obtained in 17 patients with ulcerative colitis were compared with those of 10 patients with ulcerative colitis who had undergone a colectomy, no significant correlation was detected between individual clinical and laboratory variables or the Crohn's disease activity index and in vitro tests of cell-mediated immunity. A different pattern emerged from the longitudinal tests of cell-mediated immunity: when these test results were initially abnormal in patients with Crohn's disease, clinical improvement as assessed by the Crohn's disease activity index was associated with normalizing cell-mediated immunity. In contrast, when the test results were initially normal, clinical improvement was not associated with any change in the immune response. Following colectomy in patients with ulcerative colitis, some abnormalities of suppressed immune responses remained, although patients were cured of their disease. Factors other than clinical disease activity may be responsible for the suppressed immunoresponsiveness in some patients with inflammatory bowel disease, and variable changes in cell-mediated immunity occur after both surgical and medical treatment.

(Lyanga J, Davis P, Thomson ABR: Immunoresponsiveness in ulcerative colitis and Crohn's disease—Effect of colectomy and suppression of disease activity. West J Med 1988 Apr; 148:421-425)

It is possible to show abnormalities in immunologic test results in varying proportions of patients with inflammatory bowel disease.[1-5] The role of these abnormalities in the etiology and pathogenesis of ulcerative colitis and Crohn's disease remains unclear, however, and it is unknown whether these changes are primary or secondary to the underlying inflammatory process, the treatment of the disease, or the presence of associated nutritional deficiencies.[6] We have previously found evidence of depressed cell-mediated immunity in most patients with inflammatory bowel disease, based on results of in vitro immunologic testing.[1] We have now done serial tests of the function of thymus-derived lymphocytes and K cells in patients with Crohn's disease and ulcerative colitis, before and after treatment resulting in improvement in clinical condition.

Materials and Methods

Patients

A total of 60 patients were studied; half were admitted to hospital and half were seen as outpatients. Standard clinical, radiologic, and histologic criteria were used to diagnose Crohn's disease in 33 patients and ulcerative colitis in 27.[7] There were equal numbers of men and women; the mean age was 30 years, with a range of 16 to 75 years. Age, sex, and frequency distribution of Crohn's disease and ulcerative colitis were similar to those reported in other studies.[8-10] All the patients were ambulatory and not currently in hospital, and none were considered clinically malnourished or to have hypoalbuminemia or lymphopenia. The patients were on standard regimens of treatment: 50% were receiving sulfasalazine (Salazopyrine) plus prednisone; 20% were receiving either sulfasalazine or prednisone alone. No patients were receiving azathioprine or other immunosuppressive drugs. At the time of initial testing of cell-mediated immunity, the patients had mild to moderate disease activity, as reflected by a mean Crohn's disease activity index of 168. The dose of prednisone or sulfasalazine was modified up or down, in accordance with the guidelines established in the National Cooperative Crohn's Disease Study so as to achieve improved ratings on the Crohn's disease activity index. While the dose of medication was modified over the three-month interval, no new medications were introduced. In some patients the administration of prednisone and sulfasalazine was discontinued between the beginning and the end of the study. When evaluating the changes in cell-mediated immunity, the therapeutic status of each patient was analyzed at the time of each individual testing. None of the patients had undergone a surgical procedure within one year, and none had clinical or laboratory evidence of liver or renal disease. Of the 27 with ulcerative colitis, 10 had undergone a colectomy two to ten years previously and currently had normally functioning ileostomies and were on no medication regimen.

Six patients with ulcerative colitis were followed for three months, with clinical disease activity decreasing during this time as a result of medical management, and 23 patients with Crohn's disease were similarly followed. These patients

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ABBREVIATIONS USED IN TEXT

Con A = concanavalin A
FCS = fetal calf serum
PHA = phytohemagglutinin
SK-SD = streptokinase-streptodornase

formed the basis of a subset of subjects who were investigated over a time span of three months to assess the effects of medical treatment and disease remission on in vitro testing of cell-mediated immunity.

The activity of the inflammatory bowel disease was assigned a score according to the method of Best and colleagues.[11] From a subset of a number of variables fulfilling a combination of constraints, these workers used a multiple-regression computer program to derive an equation for the prediction of a physician's overall ratings of how well a patient with Crohn's disease was doing. This equation, numerically simplified and using selected predictor variables, is the Crohn's disease activity index. Most of the predictor variables, such as number of liquid or soft stools, the presence of abdominal pain, general well-being, and extraintestinal complications, are experienced with at least equal frequency in chronic ulcerative colitis, whereas other predictor variables, such as the presence of an abdominal mass or perianal disease, are distinctly less common. For convenience, an activity index was calculated by the same method for both Crohn's disease and chronic ulcerative colitis, but these indices are not directly comparable. Furthermore, it is not yet possible in ulcerative colitis to designate a numeric value for the activity index representing mild, moderate, or severe disease. The patients with ulcerative colitis who had undergone colectomies had "inactive" disease because the disease process had been removed surgically.

Cellular Immune Studies

The cellular immune study techniques have been published previously.[1] Lymphocytes were isolated by centrifugation on Ficoll Hypaque[12] and washed three times in M199 with 10% fetal calf serum (FCS). Cells were cultured in pooled AB serum. Laboratory test results were reported three months later in 16 patients when the Crohn's disease activity index had fallen from a mean of 168 to 105.

Lymphocyte Transformation

Lymphocyte concentrations were adjusted to 1×10^6 cells per ml for streptokinase-streptodornase (SK-SD), these being optimum for our laboratory. Cells were suspended to RPMI 1640 (Grand Island Biological Col, Burlington, Ontario); cell suspensions were distributed into flat-bottomed microtiter plates. Mitogens or antigens were added to cell suspensions in triplicate.[13,14] The cells were cultured for 144 hours for both mitogens and antigens. Six hours before harvesting, 10 μl of tritiated thymidine was added to the cultures (concentration 20 Ci per ml, specific activity 40 mCi per nmol). Viability of cultures was routinely determined by the uptake of trypan blue stain in the remaining cells and by checking the yield of lymphocytes in unstimulated cells in parallel with stimulated cells. The cells were harvested using a multisample, semi-automated harvester (Skatron, Lierbyen, Norway).

Cultures of unstimulated cells from the same patient were made at all times to determine the rate of spontaneous transformation. The optimal concentrations of mitogens and antigens for lymphocyte transformation in our laboratory have previously been determined in a random selection of six normal subjects and six subjects with inflammatory bowel disease. In these groups there was no discernible difference in optimum doses, which were phytohemagglutinin (PHA; Difco Laboratories, Detroit), 14 μg per ml; concanavalin A (Con A; Calbiochem, Los Angeles), 45 μg per ml; streptokinase-streptodornase (Lederle Products, Montreal), 24 to 45 units per ml.

After harvesting, the fiber discs were removed, placed in 10 ml of scintillation fluid, and the emissions counted in a Beckman L.S. 120 scintillation counter. Results were expressed as the log of the ratio between stimulated and unstimulated cells from the same subject.[15]

K-Cell Activity

Targets. A monolayer of human amnion embryo cells was infected with herpes simplex virus type 1 and harvested at 24 hours. Normal, uninfected cells and infected cells were removed from the culture flask with 0.25% trypsin, then washed and labeled with chromium 51 for two hours at 37°C. Targets were washed four times in Ca^{2+} and Mg^{2+} free Hanks solution with 10% FCS[16,17]; 25×10^6 lymphocytes were incubated with 25×10^4 targets in the presence of 0.1 ml of serum from a herpes simplex plus control for three hours at 37°C. After incubation, 1 ml of cold media was added to neutralize the mix. The tubes were centrifuged and the supernatant decanted. The supernatant and pellet were counted and specific ^{51}Cr release was calculated after correction for the mean background release—about 5%.

Statistical methods. The statistical significance of the difference between the means of groups was determined by the method of paired and unpaired samples. Analysis of variance was done by multiple range and student Newman-Keuls procedures. The correlation coefficient and discriminant function were also computed.[18(p191),19]

The normal range of values of the many in vitro tests of cell-mediated immunity was determined in a group of 66 healthy control personnel. The results of tests of cell-mediated immunity in patients with idiopathic ulcerative colitis or Crohn's disease were compared with these normal values. For any given test, the magnitude of abnormalities was assessed by comparing the mean values of normal subjects with the mean value of the group with idiopathic ulcerative colitis or Crohn's disease. Because of the nongaussian distribution of the results of the test of lymphocyte transformation, these results were expressed logarithmically.[15]

On a day-to-day basis, repeated testing of patients over a one- to three-day span or examining the same patient's cells in triplicate or quadruplicate showed that the variation was small within either the normal or the abnormal range.

Results

Mitogen and Antigen T-Cell Proliferation

Lymphocyte transformation responses to PHA were significantly reduced in patients with unoperated ulcerative colitis and Crohn's disease when compared with normal subjects (Table 1). In the case of ulcerative colitis patients with colectomies, this abnormality was reversed. With the mitogen Con A, the suppression in transformation responses was notable in all three groups when compared with normal subjects. In contrast to the PHA responses, there was no difference between the ulcerative colitis and the ulcerative

TABLE 1.—*In Vitro Testing of Immunoresponsiveness in Control Subjects, Patients With Ulcerative Colitis, and Patients With Ulcerative Colitis Following Panproctocolectomy (Mean ± Standard Error of the Mean)*

Test, log	*Control Subjects, N=66*	*Ulcerative Colitis, Colectomy, N=10*	*Ulcerative Colitis, No Colectomy, N=17*	*Crohn's Disease, N=33*
Phytohemagglutinin				
50	1.32±0.07	1.53±0.1	1.11±0.17†	0.86±0.18‡
100	1.43±0.07	1.64±0.1	1.17±0.10†	1.20±0.12‡
Concanavalin A				
50	1.06±0.12	0.70±0.22	0.63±0.18	0.64±0.13
100	0.97±0.15	0.37±0.23*	0.70±0.19	0.48±0.15
Streptokinase-streptodornase				
50	0.54±0.08	0.04±0.13*	0.24±0.09	0.11±0.12
100	0.47±0.09	0.07±0.10*	0.15±0.10	0.02±0.10
K-Cell activity	44.8±2.5	45.7±7.9	46±4.9	42±3.48

*The mean of the value of control subjects was statistically different from the mean value in the ulcerative colitis-colectomy group ($P<.05$).

†The mean value in the ulcerative colitis-colectomy group was statistically different from the mean value in the ulcerative colitis-no colectomy group ($P<.05$).

‡The mean value in the ulcerative colitis-colectomy group was statistically different from the mean value in the Crohn's disease group ($P<.05$).

TABLE 2.—*Repeat In Vitro Testing of Immunoresponsiveness in Patients With Ulcerative Colitis and Crohn's Disease (Mean ± Standard Error of the Mean)*

	Ulcerative Colitis			*Crohn's Disease*		
Test, log	*Patients, No.*	*First Testing*	*Second Testing*	*Patients, No.*	*First Testing*	*Second Testing*
Phytohemagglutinin						
50	6	1.0±0.33	0.9±0.33	23	0.33±0.3	1.03±0.25*
100	6	1.1±41	1.1±19	23	0.73±0.22	1.43±0.18*
Concanavalin A						
50	6	0.9±0.33	1.1±0.33	23	0.51±0.28	1.45±0.26*
100	6	0.8±0.49	1.1±0.29	23	0.24±0.37	1.58±0.26*
Streptokinase-streptodornase						
50	6	0.5±0.22	0.6±0.45	19	0.11±0.20	0.31±0.29
100	5	0.3±0.35	0.9±0.65	10	0.18±0.23	0.40±0.20
K-Cell activity	5	30.4±12.0	33.6±8.13	10	47.7±5.38	32.5±4.10*

*The mean value in the second testing was statistically different from the mean value in the first testing ($P<.05$).

colitis with colectomy groups. Similar trends were noted with the antigen SK-SD. Substantial suppression of transformation responses was confirmed in active ulcerative colitis and Crohn's disease, with the degree of abnormality most noticeable in those with Crohn's disease. In addition, these results show that in two of the three stimuli (Con A and SK-SD), the suppression in the response seen in active ulcerative colitis disease was not normalized by colectomy.

K-Cell Activity

No suppression of K-cell activity was noted in any of the three groups tested when compared with normal subjects (Table 1). No differences were noted between those with ulcerative colitis with or without colectomies.

Serial Studies

The difference between the first (baseline) and second (longitudinal) testing in 6 patients with ulcerative colitis and 23 patients with Crohn's disease after at least three months of disease-suppressive therapy is shown in Table 2. The suppressed responses were initially more profound in the selected patients with Crohn's disease when compared to the selected ulcerative colitis patients. In those subjects with ulcerative colitis, a tendency to normalization of suppressed responses was noted, and although in the small number studied there was no statistically significant difference between the first and second testing, levels in the normal range were seen at second testing with both Con A and SK-SD.

In distinct contrast, the more profound abnormalities noticed at first testing in patients with Crohn's disease were reversed to a statistically significant level at second testing ($P<.05$), reaching normal levels with both Con A and SK-SD. In these patients, K-cell activity was also reduced at second testing.

The results of T-cell stimulation in patients with Crohn's disease were further analyzed by subdividing the data into two groups: those subjects whose tests were initially abnormal and those whose tests were initially normal. Of the eight Crohn's disease patients whose PHA responses were initially low, subsequent normalization occurred in seven. Of the 15 whose PHA responses were initially normal, 14 remained normal on subsequent testing and one became abnormal (Figure 1). The increase in the initially abnormal tests was statistically significant ($P<.05$), whereas the change in the initially normal tests failed to achieve statistical significance. The same can be said for optimum concentrations of Con A. Ten patients initially had suppressed responses, with a good correlation between those patients who had a suppressed

response to Con A and PHA. Of those ten, nine had normal results at retesting and one result remained abnormal. A further 11 patients had normal responses on initial testing, and these remained normal at repeat testing.

Correlation Between Clinical and Laboratory Variables

A correlation was sought between the results of each test shown in Table 2 and a wide range of clinical and laboratory variables. In both disease groups, there was no statistically significant correlation between the disease activity index and the individual values in any of the groups of tests of cell-mediated immunity. This lack of correlation existed for both first and second testing and when only those patients with abnormal values were considered. Furthermore, analysis of the therapeutic status at the time of each individual testing—baseline and longitudinal—failed to show a clear association between the changes in the tests of cell-mediated immunity and the medical regimen used. For example, in patients initially taking prednisone, the cell-mediated immunity was no different than in those patients not taking prednisone. Furthermore, a change in the dose of prednisone over a three-month interval was not associated with a directionally consistent change in cell-mediated immunity, regardless of whether the baseline test was normal or abnormal. Thus, the altered immune cellular assays were not a function of the dose of prednisone.

Discussion

In patients with Crohn's disease and ulcerative colitis, in vitro lymphocyte transformation responses to mitogens and antigens and proportions of subpopulations of circulating lymphocytes may differ from those seen in normal persons.[1,20-22] The factors that lead to this suppression of immunoresponsiveness are not clearly defined, but there are probably several, including possibly malnutrition[6] or changes in disease activity. This study evaluates the role of colectomy in patients with ulcerative colitis and the effect of medical treatment in both ulcerative colitis and Crohn's disease by measuring in vitro lymphocyte transformation responses to mitogens and antigens and K-cell activity before and after treatment. These studies were done on peripheral blood lymphocytes rather than on gut-associated lymphoid tissue. When the functional properties of T and B cells from human mesenteric lymph nodes are compared with the properties of blood lymphocytes, there were no differences between T-cell subset fractions, but the pattern of immunoglobulin secretion of polyclonally actuated lymphocytes from mesenteric lymph nodes differed from that of peripheral blood lymphocytes in both the amount of immunoglobulin secreted and the isotope distribution.[23] We did not measure B-cell function, but it is likely that the measured changes in peripheral blood T lymphocytes reflected events that were occurring in the intestine.

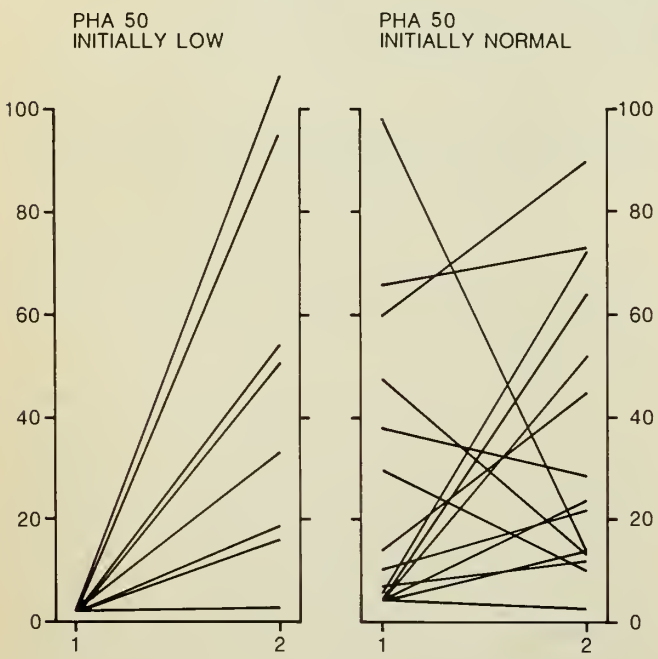

Figure 1.—Phytohemagglutinin (PHA) responses in patients with Crohn's disease. The PHA_{50} responses were determined when the patients were unwell and then on a second occasion when their symptoms had improved.

Certain trends were present that were different for individual mitogens and antigens. For example, changes that occurred with Con A and SK-SD tended to be similar in both groups of patients, whereas PHA responses tended to be different. Thus, the prevalence of suppressed immunoresponsive changes in vitro and the effects of treatment differ depending on the individual test undertaken. In addition, the level of suppression of immunoresponsiveness using such techniques was more profound in patients with Crohn's disease than in those with ulcerative colitis. The degree of change seen in our patients would suggest that the defect in immunosuppression in Crohn's disease may be a more important etiologic factor than that seen in ulcerative colitis. Such a consideration must be made cautiously, however, since in this study the baseline values in ulcerative colitis were so much closer to normal than those in patients with Crohn's disease.

In ulcerative colitis, colectomies did not appear to alter the suppressed immune responses to Con A and SK-SD, although PHA responses rose above those seen in normal persons. The suppressed responses to all three mitogens and antigens and their failure to change following colectomy suggest that although the diseased section was removed, colectomy had not eradicated the factor(s) responsible for the altered cell-mediated immunity. Alternatively, immune function may have been abnormal before colectomy and may have remained so despite removal of the diseased section.

Other workers[4] have shown that cutaneous anergy to dinitrochlorobenzene was still present after bowel resection in 6 of 10 patients (60%), while in ulcerative colitis anergy was found after colectomy in only 2 of 14 patients (14%). Tests of peripheral T and B cells studied before and after bowel resection, however, showed no difference between patients with ulcerative colitis and those with Crohn's disease.[5] The substantial abnormalities in PHA responses following colectomy observed in this study are intriguing and unexplained. Removal of the diseased bowel, weight gain, and cessation of steroid medication improve skin test reactivity but do not correct the depressed peripheral T-lymphocyte counts.[5] It was not possible in this study to evaluate the role of colectomy on PHA responses, although this is a possible factor that needs to be evaluated. It was also not possible to explore questions about fundamental differences between ulcerative colitis and Crohn's disease on the basis of preoperative and postoperative data because no patients with Crohn's disease treated surgically were included in this study.

Further evidence that the therapy for active ulcerative colitis does not primarily influence the abnormal cell-mediated immunity is seen in the patients who were tested both before and after a course of medical treatment of active ulcerative colitis. In these patients, there was no significant difference between the pretreatment and posttreatment results. Others have also suggested that the immune defect in patients with ulcerative colitis may be a secondary phenomenon.[4,5]

In patients with Crohn's disease, no correlation was observed between the baseline cell-mediated immunity and the initial value of the Crohn's disease activity index. Also, at second testing, there was no correlation. There did appear to be two subgroups of patients with Crohn's disease: those with initially normal cell-mediated immunity, and those whose baseline immunity was abnormal. In examining those two subgroups separately using longitudinal tests of cell-mediated immunity, a further difference emerged: when baseline test results were abnormal, clinical improvement was associated with more normal results on the tests of cell-mediated immunity. In the small number of patients studied, the responses, while not pronounced, were suppressed, and at second testing with both Con A and SK-SD, the responses were similar to those seen in normal subjects. At second testing in patients with Crohn's disease, there was a notable rise in responses to PHA and Con A following at least three months of medical treatment (Table 2). This effect was most pronounced when patients were initially found to have a suppressed response, which usually became normal after clinical improvement (Figure 1). These results suggest that treatment resulting in suppression of the disease process is associated with a return to normal of previously suppressed immunoresponsiveness.

The improvement in the initially abnormal immune responses may have been due to the disease process because clinical improvement was associated with immune improvement (Figure 1). The patients with initially abnormal immune responses, however, were just as sick clinically as the patients with initially normal immune responses, and their doses of prednisone and their nutritional status were comparable. Furthermore, the altered immune cellular assays were not a function of the dose of prednisone. Thus, there appear to be at least two subgroups of patients with Crohn's disease. Those with initially abnormal immunity were noted to have a dramatic improvement in cell-mediated immunity associated with clinical improvement. In contrast, in those patients with Crohn's disease who initially had normal cell-mediated immunity, the immunity remained normal when the patients' clinical condition improved. We must now examine whether the clinical course or response to treatment varies in these two immunologic subgroups of patients with Crohn's disease.

No correlation was found between changes or levels of baseline immune responses and the Crohn's disease activity index; similar results have previously been reported.[1] This suggests that changes in cell-mediated immunity either toward or away from normalcy are not reflected by variations in selected clinical features of the disease. We must stress that our group of patients had only mild to moderate disease activity, and that more substantial changes in the activity index might have been associated with greater changes in cell-mediated immunity. Thus, the change in the activity index in this study from a mean of 168 to 105 may show an insufficient alteration in disease activity to be reflected by a change in cell-mediated immunity. The alternative explanation is that the Crohn's disease activity index reflects factors other than those responsible for the underlying disease process and under these circumstances need not be expected to reflect primary etiologic factors in the pathogenesis of the disease.

Indeed, the topic of the assessment of Crohn's disease activity has recently been reviewed,[11] and the use of the Crohn's disease activity index has been criticized.[4] In claiming a favorable response to the use of prednisone and sulfasalazine as assessed by their effect on the Crohn's disease activity index, a nonspecific effect on at least four of the eight variables used in the index cannot be totally dismissed as a possible explanation.[13] The measurement of serum albumin and seromucoid has been suggested to be of use in distinguishing between the extremes of the clinical states of relative health and well-being.[5] The serum albumin concentrations were all greater than 3.5 grams per dl in our patients with Crohn's disease, and measurements of serum seromucoid were not available to us.

We conclude that factors other than just the disease activity are responsible for the suppressed immunoresponsiveness in patients with inflammatory bowel disease and that variable changes in this in vitro test occur subsequent to both surgical and medical treatment.

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Clinical Medicine

Hepatocellular Carcinoma in Hepatitis B Surface Antigen Carriers in Eight Institutions

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We reviewed records of all persons dying between 1979 and 1986 in eight California institutions for the mentally retarded. Autopsies had been done in 71% of the 1,181 deaths. Nine deaths were due to hepatocellular carcinoma, which invariably developed in carriers of hepatitis B surface antigen (HBsAg) and was fatal within four months of diagnosis. The mean age at death was 32.7 years. The incidence of hepatocellular carcinoma in HBsAg carriers was 140 times greater than in the US population. Persistent hepatitis B infection was probably etiologically related to hepatocellular carcinoma in this population, which is relatively free of exposure to other hepatocarcinogens.

(Lohiya GS, Pirkle H, Nguyen H, et al: Hepatocellular carcinoma in hepatitis B surface antigen carriers in eight institutions. West J Med 1988 Apr; 148:426-429)

Hepatocellular carcinoma is the most common malignant neoplasm in Asia and Africa, but it is uncommon in the United States.[1-5] It ranks 22nd among malignant diseases in white men in the US.[4] Persistent infection by hepatitis B virus (HBV) is considered etiologically related to more than 80% of cases of hepatocellular carcinoma. In a Taiwanese population study, the relative risk of hepatocellular carcinoma in carriers of hepatitis B surface antigen (HBsAg) was estimated to be 223 times greater than in noncarriers.[2] Clients of institutions for the mentally retarded, because of a 10% to 12% HBsAg positivity rate,[6-8] form a population apparently predisposed to this carcinoma. It has been noted, however, that immunologically compromised children who acquire HBV infection early in life in institutions rarely have hepatocellular carcinoma.[5] Our study was undertaken to determine the incidence in mentally retarded persons in institutions and to see if the heightened risk for hepatocellular carcinoma found in men in the Far East applies to HBsAg carriers of other races in different geographic areas and to women as to men.

Methods

We reviewed all deaths of institutionalized persons occurring between January 1979 and December 1986 to identify cases of hepatocellular carcinoma. This study involved all of the eight institutions in California, officially called developmental centers: southern (Fairview, Camarillo, Lanterman), central (Porterville), and northern (Sonoma, Napa, Stockton, Agnews). These institutions are state-operated, long-term skilled nursing and intermediate care facilities for developmentally disabled clients. General features of the population have been described previously.[6,7] About 70% are profoundly mentally retarded (intelligence quotient less than 25); 27% are severely mentally retarded (intelligence quotient 25 to 39); and 3% have cerebral palsy, autism, or severe epilepsy. The most common cause of mental retardation (92%) is some unknown prenatal influence; 7% have Down's syndrome; and 1% have suffered postnatal hypoxia, such as near drowning.

Pursuant to a state law effective in January 1979, all deaths in state institutions are subject to a coroner's inquest. Consequently, autopsies have been done frequently, and causes of death have been recorded with the utmost diligence. The autopsy frequently includes microscopic examination of the brain, heart, lung, liver, spleen, kidney, stomach, intestines, muscles, adrenals, and thyroid.

As part of their health examination, most clients have been screened annually since 1972 for HBsAg by increasingly more sensitive methods: counterimmunoelectrophoresis (1972 to 1978), reverse passive hemagglutination (1978 to 1981), radioimmunoassay (1981 to 1984), and enzyme-immunoassay (since 1984). They have also been tested annually for serum levels of alanine aminotransferase (ALT, formerly SGPT). Since 1985, HBsAg carriers have been screened annually for serum α-fetoprotein (AFP) by monoclonal radioimmunoassay.

For the study period, we reviewed all death certificates and autopsy reports to determine the immediate and underlying causes of death. In all cases of a hepatic malignant disease, liver tissue slides were retrieved when available and reexamined by a pathologist (H.P.) for morphologic verification of the diagnosis and for determination of associated hepatic pathology such as liver cirrhosis and chronic active hepatitis. Medical records of hepatocellular carcinoma cases were reviewed to identify age, sex, race, HBsAg status, exposure to any potential hepatocarcinogen, cause and severity of mental retardation, and duration in institutions.

Results

The mid-year client census for the eight study years was 9,114, 8,742, 8,385, 8,270, 7,880, 7,562, 7,430, and 6,998, for a total of 64,381 person-years. There were 1,181

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ABBREVIATIONS USED IN TEXT

AFP = α-fetoprotein
ALT = alanine aminotransferase
HBsAg = hepatitis B surface antigen
HBV = hepatitis B virus

client deaths between 1979 and 1986, for a crude death rate of 18.3 deaths per 1,000 per year. Mean age at death was 23 years, 58% were men; 83% were white, 7% black, 6% Hispanic, and 4% other races.

Autopsies were done in 833 (71%) deaths; the liver was examined microscopically in 741 (63%) deaths. Results of HBsAg screening were available for 844 of those who died; 66 (8%) were HBsAg-positive and 778 (92%) were HBsAg-negative (Table 1). For 337 subjects, HBsAg screening had not been done due to an inability to obtain a blood specimen—sudden death, difficult veins in underweight infants—or lack of a universal screening protocol in the early years covered by the study.

Common causes of the 1,181 deaths were bronchopneumonia and aspiration pneumonia, 626 (53%); other cardiopulmonary disorders, 153 (13%); choking and other accidents, 118 (10%); and miscellaneous conditions, 284 (24%). Neoplasms were found in 67 clients: hepatocellular carcinoma in 9; gastrointestinal, 8; brain, 7; leukemia, 6; lymphoma, 5; breast, 5; prostate, 5; kidney, 4; skin, 4; uterus, 3; ovary, 3; testis, 3; muscle, 3; lung, 1; and bone, 1.

Of the 66 HBsAg carriers in our study, 9 had hepatocellular carcinoma. HBsAg carriers with this disorder were comparable to carriers without it with reference to age, sex, race, and duration in institutions. All clients with hepatocellular carcinoma were HBsAg carriers, nonsmokers, and consumed less than one alcoholic drink per month. They had not been exposed to hepatocarcinogens, such as androgenic steroids, vinyl chloride, or thorotrast—a colloidal preparation of thorium dioxide—and did not have hepatic parasites. Their brief case reports are presented in Table 2. The mean age of clients with hepatocellular carcinoma was 32.7 years, with a range of 21 to 52 years. Seven cases occurred in men and two in women; eight were white and one was US-born Asian. Cirrhosis was present in only two cases. In two, hepatocellular carcinoma was diagnosed at autopsy after sudden death.

In all cases of hepatocellular carcinoma, the clinical course was one of rapid deterioration and death within four months after diagnosis. Clinical features included hepatosplenomegaly, jaundice, ascites, hepatic coma, cachexia, and metastases. The serum ALT level remained normal until late in most cases.

In one case (case 9, Table 2), a suspicion of hepatocellular carcinoma was first raised because of an abnormal serum AFP level. A liver scan showed an isolated nodule measuring 1.5 cm. The patient underwent hepatic lobectomy two months later. Following an uneventful postoperative period of ten days, the patient died of a hepatorenal syndrome.

Discussion

In this study, almost total certainty of the cause of death was assured by conducting a coroner's inquest in all deaths and doing an autopsy in 71%. Hepatocellular carcinoma was a common cause of death from cancer at a young age in this study population, with a case-fatality rate of 100%. For comparison, hepatocellular carcinoma ranked 22nd in incidence

TABLE 1.—*Study Population Stratified by Status for Autopsy and Hepatitis B Surface Antigen (HBsAg)*

	All Clients	*HBsAg-Positive*	*HBsAg-Negative*	*HBsAg Unknown*
Total deaths, No.	1,181	66	778	337
Total autopsies, No.	833	56	571	206
Gross and microscopic examination of liver done at autopsy	741	52	516	153
Only gross examination of liver, no microscopic examination	92	4	55	53

of malignant diseases in the general US population.[4] All cases of the carcinoma occurred among the 66 HBsAg carriers who died. In contrast, none occurred in clients who were HBsAg-negative or whose HBsAg status was undetermined ($P < .01$). The occurrence of these nine cases of hepatocellular carcinoma in 64,381 person-years is equivalent to an incidence ($9 \div 64{,}381 \times 100{,}000$) of 13.98 cases per 100,000 clients per year. Throughout the study period, the HBsAg prevalence in the clients ranged between 9.5% and 10.5% (mean 10%); of the 64,381 person-years, 10% or 6,438 person-years represent HBsAg carriers. The incidence of hepatocellular carcinoma in HBsAg carriers was, therefore, $9 \div 6{,}438 \times 100{,}000$, or 139.8 cases per 100,000 carriers per year, which is 140 times greater than the incidence of hepatocellular carcinoma in the US population—1.0 case per 100,000 population per year. This observation is similar to relative risk estimates obtained in a Taiwanese population study[2] and contradicts the reported rarity of hepatocellular carcinoma in institutionalized persons.[5] It is conceivable that the incidence in the institutionalized mentally retarded would be much higher if their mean life span were not so short (mean age at death for all clients is 23 years) and if more autopsies were done—in two clients, hepatocellular carcinoma was first identified at autopsy (see Table 2).

Hepatocellular carcinoma in adults in the US is largely a disease of 50- to 70-year-olds, with a strong predominance in men. More than 80% of cases are associated with alcoholic cirrhosis. In contrast, in this study the mean age of the nine clients with this disorder was 32.7 years; two were women, and none had alcoholic cirrhosis.

In this population, HBV infection was probably acquired during late childhood or early teens, soon after the profoundly mentally retarded client became hard to care for at home and was institutionalized.[6,8] Because the HBsAg-positivity rate in the United States population is low (0.2%), it is unlikely that those in our study acquired HBV infection in the perinatal period or in early childhood from household contacts. The interval between institutionalization and the development of hepatocellular carcinoma for these nine cases was 12, 19, 33, 18, 24, 29, 24, 19, and 38 years (see Table 2). Assuming that hepatitis B infection occurred immediately after institutionalization, it took a mean latent period of 24 years for hepatocellular carcinoma to develop. These data are important when evaluating the risk for Americans acquiring hepatitis B infection as adults, such as intravenous drug users, homosexual men, and health care personnel.

Recently, a relatively less malignant and distinct clinicopathologic subset of this disorder, fibrolamellar oncocytic hepatocellular carcinoma, has been described.[9] This variant is unrelated to HBV infection and is characterized by a longer duration of symptoms, high resectability rate, the presence of lamellar bundles of collagen, and infrequency of mitoses.

None of these features were present in the nine cases reported here, which were probably related to HBV infection.

The role of cocarcinogens in human hepatocellular carcinoma is uncertain.[1,2] Aflatoxins—potent hepatic carcinogens in animals—are frequently present in foodstuffs in areas with high incidences of this carcinoma. It is hypothesized that aflatoxins suppress cell-mediated immunity and thereby permit HBV to maintain itself in the liver and eventually produce hepatocellular carcinoma.[10] Because of the complexity of the Chinese diet, the role of aflatoxins was not evaluated in the study of liver cancer in Taiwan.[2] In our study, the nine clients with hepatocellular carcinoma were born in the US and while institutionalized had consumed meals planned by certified dietitians. The aflatoxin content of foodstuffs in the US is low because of superior farming and crop storage techniques.[10] Moreover, the aflatoxin content of foods served to clients at the Fairview institution has been assayed by thin-layer liquid chromatography (G.S. Lohiya, unpublished data, September 1985 to March 1986). None of 36 samples during three seasons contained aflatoxin above 20 parts per billion, the "safe" level permitted by the US Food and Drug Administration.[11] In a detailed review of medical records of all clients with hepatocellular carcinoma, no evidence was found of exposure to other hepatocarcinogens.

The crude death rate for this population (with a mean age of 23 years) was 18.3 per 1,000 per year. The death rate for those aged 20 to 24 years in the US is 1.3 per 1,000 per year.[12(p429)] Thus, the death rate for these clients is 14 times higher. This is probably due to an extremely high incidence of respiratory infections and aspiration pneumonia in retarded

TABLE 2.—*Clinicopathologic Features of Clients Dying of Hepatocellular Carcinoma (HCC)*

Subject No.	*Age at Death, Sex, Race, Body Weight*	*Tenure in Institute, Year of Death*	*Duration of Known Hepatitis B Carriage*	*Clinical Features*	*Pathologic Features*
1	21 yr, male, white, 57 lb	12 yr, 1979	7 yr	Sudden death due to peritoneal hemorrhage (abdominal pain, shock); previously asymptomatic	Liver weight 1,300 grams, large yellow friable tumor in right lobe; moderately pleomorphic anaplastic cells, grade 3 trabeculoacinar type, fibrosis with lymphocytic infiltration, portal bridging but no cirrhosis
2	31 yr, male, Asian, 142 lb	19 yr, 1980	8 yr	Down's syndrome; previously asymptomatic; death after accidental fall due to pulmonary embolism by tumor emboli	Liver weight 2,350 grams, studded with multiple yellow tumor nodules, well-differentiated, trabeculoacinar type grade 2, nuclear pleomorphism; piecemeal necrosis, lymphocytic infiltration and portal bridging present
3	33 yr, male, white, 136 lb	33 yr, 1982	9 yr HBeAg+	Hepatosplenomegaly 3 mo before death; liver biopsy and CT scan revealed massive incurable HCC of right lobe; death due to cachexia	Liver weight 3,300 grams, studded with numerous discrete tumor nodules measuring up to 1.5 cm; trabeculoacinar type, nuclear pleomorphism
4	26 yr, male, white, 60 lb	18 yr, 1983	6 yr	Ascites 3 mo before death; serum AFP 206,500 ng/ml; inoperable tumor; progressive cachexia, lethargy, and death	Liver weight 1,800 grams, studded with nodular white masses, tumor cells, polygonal in trabeculae, hemorrhage, necrosis, mild portal fibrosis without lymphocytic infiltration
5	27 yr, male, white, 104 lb	24 yr, 1983	7 yr	Hepatosplenomegaly 3 mo before death, CT scan revealed multiple tumor nodules in liver; ascites and hepatic encephalopathy developed	Liver weight 3,750 grams, large multiple tumor nodules measuring up to 4 cm, cut surface was ivory to yellow with hemorrhage and necrosis; nuclear pleomorphism; trabeculoacinar
6	37 yr, male, white, 143 lb	29 yr, 1984	12 yr	Hepatomegaly, ascites 3 mo before death; serum AFP 145,000 ng/ml; CT scan revealed large tumor; died of intestinal bleeding, sepsis, and hepatic coma	Liver weight 2,550 grams; large solitary tumor with necrosis and hemorrhage; tumor extended to inferior vena cava and mostly replaced the liver; multifocal, lymphocytic infiltration; no cirrhosis
7	29 yr, female, white	24 yr, 1985	12 yr	Ascites and edema 4 mo before death; CT scan revealed hepatosplenomegaly with multiple well-defined nodules, serum AFP 1,500 ng/ml, which increased to 12,500 ng/ml 72 days later; died of hepatic encephalopathy and cachexia	Multifocal trabecular HCC with moderate nuclear pleomorphism and cirrhosis
8	38 yr, male, white	19 yr, 1986	5 yr	Down's syndrome; jaundice, ascites, hypoglycemia, and elevated serum ALT developed a month before death; serum AFP 334,000 ng/ml 18 days before death; CT scan revealed notable hepatomegaly due to multiple tumor nodules; died of hepatic coma and cachexia	Large liver almost totally replaced by yellow and white tumor masses
9	52 yr, female, white	38 yr, 1986	10 yr	Clinically asymptomatic; serum AFP abnormal: 38 ng/ml (Dec 1984), 125 ng/ml (Oct 1985), 610 ng/ml (Jan 1986); liver scan normal Oct 1985; in Mar 1986, scan showed 1.5 cm smooth round tumor in right lobe of liver; right hepatic lobectomy done in June 1986; died 10 days later of hepatorenal syndrome	Large liver; tumor measured 1.8×1.8 ×1 cm; parenchyma cirrhotic; large pleomorphic tumor cells, mixed nodular cirrhosis, fatty change; portal areas full of lymphocytes

AFP=α-fetoprotein, ALT=alanine aminotransferase, CT=computed tomographic, HBeAg=hepatitis B e antigen, HCC=hepatocellular carcinoma

clients, many of whom are bedridden.

The observation of a high incidence of hepatocellular carcinoma among HBsAg carriers in a US population free of exposure to other hepatocarcinogens (such as aflatoxin, tobacco smoke, ethanol, vinyl chloride, hepatic parasites) greatly strengthens the etiologic link between persistent hepatitis B infection and hepatocellular carcinoma. Mental retardation per se is not known to predispose one to this disorder, other than by exposing a client to hepatitis B infection in institutions.

There is no effective cure for the HBsAg carrier state, and the carriers—about 200 million worldwide—are at a 0.3% to 0.7% annual risk of hepatocellular carcinoma developing.[10] Primary prevention should be attempted by vaccination for hepatitis B of all susceptible high-risk groups. Secondary prevention could be achieved by early diagnosis of this disease with semiannual α-fetoprotein screening of all HBsAg carriers and follow-up of all persons with abnormal results with serial ultrasonography. Both of these forms of prevention are currently being undertaken in the California institutions.

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Tuberculosis

BEWARE OF TUBERCULOSIS. Tuberculosis is present; it has never decreased in frequency; it has only decreased in mortality and morbidity because we have antituberculosis drugs.

I would hate to tell you how many times we see tuberculosis—active tuberculosis—at autopsy and in a patient who has been in the hospital for six months, being treated with any number of mega antibiotics—every antibiotic you can think of, except the one for tuberculosis.

When I teach residents and medical students about diseases in the elderly, I tell them, "You've got to be careful of two things and both of them begin with T—tuberculosis and tumor." Never forget that tuberculosis is not an uncommon disease in the elderly. Never forget that the tuberculin test may be negative in those of increasing age and that 40% of people who have tuberculosis have negative chest x-ray films. So tuberculosis is an absolutely necessary consideration in every elderly patient!

—ALBERT S. KLAINER, MD

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Motor Neuron Disease in the Rocky Mountain Region

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We saw 166 patients with motor neuron disease over a ten-year period, 116 with amyotrophic lateral sclerosis—111 sporadic and 5 familial—and 50 with progressive muscular atrophy. The age at onset varied widely, with the youngest mean onset occurring in the familial group. The most common presenting symptoms were leg or arm weakness and difficulty speaking or swallowing; fewer patients reported cramping, fasciculation, or fatigue. Mean survival time was less in familial cases, women, older patients, and in those with difficulty speaking and swallowing. A total of 50% of all patients were alive after four years; 13% were alive after ten years. Previous reports on the natural history of motor neuron disease may be overly pessimistic in suggesting that survival time rarely exceeds two years.

(Smith LD, Kenny CE, Ringel SP, et al: Motor neuron disease in the Rocky Mountain region. West J Med 1988 Apr; 148:430-432)

The adult motor neuron diseases are a group of hereditary or acquired disorders characterized pathologically by progressive degeneration of the motor neurons required for voluntary movement. Loss of motor neuron innervation leads to atrophy and weakness of the cranial, trunk, or limb muscles, while intellect and perception are spared.

Motor neuron disease includes several major subcategories.[1,2] In amyotrophic lateral sclerosis (ALS) muscle atrophy is combined with signs of pyramidal tract dysfunction, including spasticity, hyperreflexia, or Babinski's signs; the majority of cases occur sporadically, although some are familial. Progressive muscular atrophy (PMA) is a sporadic adult illness where muscle atrophy and weakness are prominent. There are no clinical signs of pyramidal tract dysfunction, although pyramidal lesions may be present pathologically. Spinal muscular atrophies (SMA) are recessively inherited disorders with onset from infancy through early adulthood. Spinal muscular atrophy resembles the progressive disorder, except for its purely familial occurrence and more favorable prognosis.[3]

There is a cumulative loss of motor neurons, increasing disability, and death in all forms of motor neuron disease,[4-6] although the rate of progression varies widely. In this report we review the clinical characteristics and course of these disorders in 166 patients seen in a major tertiary medical facility in the Rocky Mountain region and compare the results with previous reports.

Patients and Methods

Inclusion Criteria

Patients were selected from a retrospective chart review of new cases seen at the University of Colorado Neuromuscular Clinic between 1976 and 1986. All fulfilled the clinical criteria of motor neuron disease[5] and had confirmation of neurogenic muscle disorder by electromyogram or muscle biopsy.

Patients were classified into three groups based on clinical findings: 111 patients in the sporadic ALS group had no family history of the disease and had pyramidal signs at some point during their illness; 5 patients with autosomal-dominant ALS had a family history consistent with autosomal-dominant transmission and had pyramidal signs; 50 patients in the group with progressive muscular atrophy had no family history of motor neuron disease and never had pyramidal signs. Patients with a family history of spinal muscular atrophy and without pyramidal signs were excluded. Patients with pyramidal signs unaccompanied by muscle atrophy, a prior history of polio, significant sensory loss, or other atypical neurologic signs, or any patients who improved were also excluded. Two patients with a history of ALS in other family members but without an autosomal dominant pattern of inheritance were excluded.

Analysis of Clinical Data

Age, sex, family history, presenting symptoms, and abnormal physical signs present at the first and subsequent evaluations were tabulated. All patients were given repeat examinations or follow-up status was determined by telephone contact. Duration of illness was defined as the time from the onset of symptoms to the time of death or to the latest follow-up.

Results

The mean age at onset in the three clinical groups of motor neuron disease is listed in Table 1. In the autosomal-dominant ALS group the illness developed at a slightly younger mean age. ALS developed in women at an older mean age in all three groups, as it did in patients presenting with bulbar

ABBREVIATIONS USED IN TEXT

ALS = amyotrophic lateral sclerosis
PMA = progressive muscular atrophy
SMA = spinal muscular atrophy

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TABLE 1.—*Age at Onset of Motor Neuron Disease (N=166)*

	Sporadic ALS				Autosomal-Dominant ALS				Progressive Muscular Atrophy			
		Age at Onset,				Age at Onset,				Age at Onset,		
	(No.)	Years	(range)	SD	(No.)	Years	(range)	SD	(No.)	Years	(range)	SD
All patients	(111)	56.2	(17-85)	14.0	(5)	50.6	(35-67)	14.4	(50)	54.8	(17-83)	16.5
Men	(54)	54.2	(17-85)	14.6	(2)	44.5	(37-52)	10.6	(25)	54.5	(17-83)	17.4
Women	(57)	58.1	(24-83)	13.3	(3)	54.5	(35-67)	17.2	(25)	55.2	(22-72)	16.0

ALS=amyotrophic lateral sclerosis, SD=standard deviation

TABLE 2.—*Presenting Symptoms of Motor Neuron Disease in All Categories (N=166)*

Complaint	%
Leg weakness	33
Arm weakness	21
Difficulty with speech or swallowing	20
Cramping	4
Fasciculation	3
Fatigue	2
Multiple symptoms	17
	100

symptoms (data not shown). There was no difference in the mean age at onset between patients presenting with arm or leg weakness or for patients with bulbar signs—weakness, fasciculation of cranial musculature, hyperactive gag, or jaw jerk—but free of bulbar symptoms (data not shown).

The most common presenting symptom was leg or arm weakness (Table 2). Occasionally patients reported two symptoms beginning simultaneously at the onset of illness. The relative frequency of these symptoms was similar among the three groups with the exception that bulbar symptoms and cramping were more common in patients with sporadic ALS.

Survival figures for the 166 patients are shown in Figure 1: half the patients survived at four years. The longest individual survival for each group occurred in patients who are still alive—sporadic ALS, 19 years; autosomal-dominant ALS, 3 years; PMA, 24 years.

Table 3 outlines the mean duration of illness in 75 patients who have died—55 with sporadic ALS, 3 with autosomal-dominant ALS, and 17 with PMA. The longest mean duration of illness was in the PMA group, while the shortest was in the autosomal-dominant ALS group. In all three clinical groups the mean survival was shorter in women, patients over the age of 55 years at the start of illness, and patients presenting with bulbar symptoms. There was no difference in the mean duration of illness between patients presenting with arm or leg

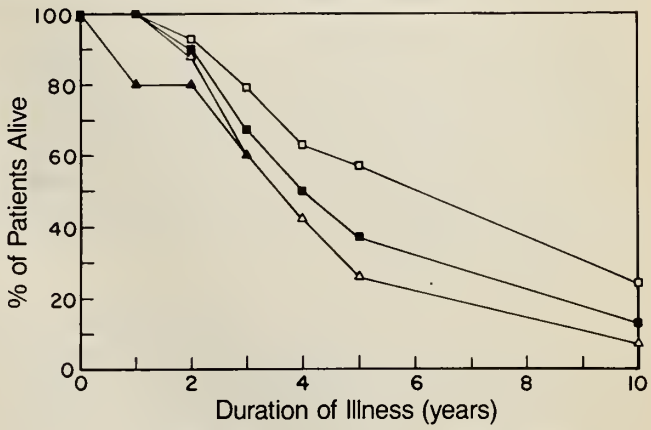

Figure 1.—The graph summarizes the duration of illness and patient survival in motor neuron disease. △ = sporadic amyotrophic lateral sclerosis; ▲ = autosomal-dominant amyotrophic lateral sclerosis; □ = progressive muscular atrophy; ■ = all patients

weakness, or for patients with signs of bulbar dysfunction but free of symptoms at the time of first evaluation (data not shown). Esophagostomy or gastrostomy had no effect on the duration of illness (data not shown).

Discussion

Previous reports of the natural history of motor neuron disease have reached disparate conclusions depending on whether the cases are selected solely from death certificates, from autopsy records, or from a population of living patients. Reports based on death certificates are more likely to select older patients,[7] while autopsy reports may reflect the most rapidly progressive cases.[6] Conversely, younger, more mobile patients and those with relatively indolent disease are more likely to receive care in a regional center and thereby be overrepresented in clinical reports.[8,9]

The referral population in our study is similarly biased but includes all patients, whether alive or dead, and we analyzed outcome according to clinical differences among the various

TABLE 3.—*Duration of Illness in Patients With Motor Neuron Disease Who Have Died (N=166)*

	Sporadic ALS				Autosomal-Dominant ALS				Progressive Muscular Atrophy			
		Duration of Illness,				Duration of Illness,				Duration of Illness,		
	(No.)	Years	(range)	SD	(No.)	Years	(range)	SD	(No.)	Years	(range)	SD
All dead patients	(55)	3.0	(1-18)	2.9	(3)	1.9	(0.8-3)	1.1	(17)	3.5	(1-11)	2.6
Men	(26)	3.7	(1-18)	3.9	(1)	3.0	...	...	(9)	4.1	(1-11)	3.2
Women	(29)	2.4	(1-5)	1.2	(2)	1.4	(0.8-2)	0.7	(8)	2.8	(2-6)	1.4
Age at onset <55 yrs	(17)	4.6	(1-18)	4.6	(2)	1.9	(0.8-3)	1.4	(3)	4.7	(1-11)	5.5
Age at onset >55 yrs	(38)	2.3	(1-7)	1.2	(1)	2.0	...	...	(14)	3.2	(1-6)	1.7
Difficulty with speech or swallowing at presentation	(18)	2.7	(1-7)	1.4	(1)	2.0	...	...	(3)	2.7	(1-5)	2.1

ALS=amyotrophic lateral sclerosis, SD=standard deviation

forms of motor neuron disease. The distinction between ALS and PMA is imperfect inasmuch as the division in some cases must be made on the basis of transient clinical signs. Some authors have not made the distinction at all,[4,7,10] and so may have unknowingly included isolated cases of adult spinal muscular atrophy, a disorder with a much longer survival time. Such patients may be included in our study, thereby increasing the number of patients with long survival. We feel confident that such patients are restricted to the group with progressive muscular atrophy, with onset before the age of 55 years.[3]

The presence of hyperreflexia or other signs of pyramidal tract dysfunction accompanied by muscle atrophy is strongly suggestive of ALS. We found this combination in more than half our patients during the initial evaluation. Pyramidal signs may develop later in the illness[4] and may disappear due to severe muscle atrophy; this occurred in eight of our patients. The proportion of our patients with progressive muscular atrophy (30%) is similar to that in previous reports,[1,11,12] as is the low incidence of familial ALS.[6,11,13,14]

Most (90%) of our patients presented with the well-recognized symptoms of limb weakness, bulbar dysfunction, or both,[5,10,11,15] although a few reported symptoms that have not been emphasized, such as cramping, fasciculation, or fatigue. As we mentioned before,[12] bulbar symptoms and cramping were particularly common in the sporadic ALS group.

Motor neuron disease is thought to be slightly more common in men than in women, with men numbering as high as 71% of the total in one report.[14] We encountered a nearly equal number of men and women for all varieties of motor neuron disease, which others have attributed to the excess number of women in the age group at risk for these disorders.[16]

The mean age at onset varied little among our clinical groups, while the range in age at onset was older than 60 years. In other studies, the mean age at onset has varied widely due to biases inherent in selection and ascertainment—from 52 years reported in a prevalence study enumerating only living patients[7] to 66 years in a review of death certificates.[16,17] Our findings agree with those in previous reports in that the youngest mean age at onset was in the autosomal-dominant ALS group,[13] and the older mean age at onset occurred in women and in all patients presenting with bulbar symptoms.[1,4,10,11]

A short survival following the onset of motor neuron disease has been emphasized in the past based on reviews of autopsy findings or death certificates.[1,16] These reports probably underrepresent younger patients and those with a long survival, since we were able to show a shorter survival by analyzing data on dead patients separately (Table 3). In contrast to the often quoted survival time of two years or less, we found that half our patients were alive four years after the start of illness (Figure 1), in agreement with other studies that included living as well as dead patients.[10,15] Most of our patients with prolonged survival times were in the PMA group,[6,12] while the shortest duration of illness occurred in the autosomal-dominant ALS group.[13]

We confirmed the poor prognosis for older patients,[10,15,16] which may result from several factors, and for patients presenting with bulbar symptoms.[4,10,14] We noted a relatively poor prognosis for women, which is perhaps due to the older mean age at onset. Older patients may ignore initial symptoms or attribute them to aging, delaying diagnosis and leading to a shorter calculated survival time.[8] In addition, medical complications may contribute to shorter survival in a population expected to have more illness than the young. Patients with bulbar involvement are predisposed to dysphagia, malnutrition, or aspiration pneumonia. The most significant factor in the poor prognosis associated with bulbar symptoms may relate to the older mean age at onset in this group, however, because patients presenting with bulbar symptoms had the same mean age at onset as the entire group and no worse a prognosis in one study.[16]

There was no difference in prognosis between patients presenting with arm or leg weakness.[6] Interestingly, we found that patients with signs of bulbar dysfunction but free of bulbar symptoms did not differ in mean age at onset and had no worse prognosis than the whole group, despite what appears to be an ominous physical abnormality.

Esophagostomy or gastrostomy were offered to those patients with severe dysphagia, malnutrition, or at risk for aspiration. Surgical modification improved the quality of life in these selected patients but did not extend life.

A few patients had prolonged survival, including those with poor prognostic features. Previous studies have noted the great variation in natural history, with 10% alive after 10 years[5] and patients rarely surviving as long as 35 years.[4] At the time of initial evaluation, these patients may be clinically indistinguishable from others who will succumb rapidly, further emphasizing the prognostic uncertainty in any individual case of motor neuron disease.

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Clinical Review

'Silk Route Disease' (Behçet's Disease)

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Behçet's disease is a multisystem disorder in which orogenital ulceration is associated with troublesome generalized uveitis, erythema nodosum, pyoderma, dermatographism, seronegative arthritis, and neurologic and cardiovascular symptoms. There is no diagnostic laboratory test; the diagnosis is based on the disorder's multisystem clinical features. A points scoring system is helpful in distinguishing it from other multisystem disorders that mimic it. It occurs most frequently in an area coinciding with the old Silk Route, between latitudes 30° and 45° north, in Asian and Eurasian populations, and it has an HLA-B51 affinity. The cause remains unknown, but a postulated trigger factor is a herpesvirus with cofactors that include ethnic group, human leukocyte antigen affinities, T-cell and autonomic imbalance, circulating immune complexes, autoimmunity, blood viscosity, decreased fibrinolysis, and zinc deficiency. Treatment includes administering corticosteroids, azathioprine, chlorambucil, cyclosporine, and colchicine, and fibrinolytic therapy.

(James DG: 'Silk route disease' (Behçet's disease). West J Med 1988 Apr; 148:433-437)

Hulusi Behçet (1889-1948), a professor of dermatology in Istanbul, died 40 years ago, leaving for posterity an eponymous multisystem syndrome that is being increasingly recognized worldwide. He described the triad of recurrent aphthous ulceration of the mouth and genitalia, relapsing uveitis, and skin lesions.[1] The syndrome may present to many different disciplines (Table 1).

Epidemiology

Behçet's disease occurs most frequently in Japan and the Mediterranean countries but also in the populations linking these two areas to each other. It occurs most commonly between latitudes 30° and 45° north in Asian and Eurasian populations. Ohno[2] has pointed out that this area coincides with the Silk Route. If Behçet's disease were renamed "Silk Route" disease, then it would at least convey epidemiologic significance.

The old Silk Route was opened during the Han Dynasty in the year 200 BC. This hazardous route was followed by Marco Polo, Genghis Khan, Chinese pilgrims, and in more recent times by that adventurous American president, Teddy Roosevelt. On May 1, 1936, it was renamed the Karakoram Highway as a friendship doorway for international tourists traveling between China and Pakistan. This joint China-Pakistan highway involved 20 years (1966-1986) of planning and construction in the most difficult terrain in the world. It is 1,233 km (766 mi) long, with a plateau 762 m (2,500 ft) high, linking Chinese highways with Pakistan, Iran, Turkey, and Europe. It also runs very close to the territories of the USSR and India's Kashmir. Anyone traveling on this modern route should spare a thought for the original Silk Route, so called because it was the pathway for the caravans of Chinese traders whose camels groaned under masses of silk as they crossed the Karakoram mountain range, well-nigh the roof of the world.

But what is the link between this geographic distribution and the multisystem disorder so frequently observed in it? It is possible that there is a background immunogenetic factor associated with the human leukocyte antigen HLA-B51.[3] Other cofactors or triggering agents may include viruses or bacteria or close contacts with pigs or pork.[4] It could also be due to the soil in the region, which, because of the climate, is unique.

Ohno notes that there are about 15,000 patients in Japan, 700 in China, about 350 each in Korea and Iran, and 1,000 in Turkey.[2] Although an immunogenetic terrain of HLA-B51 is postulated, it is not observed in the Japanese living in San Francisco or Hawaii. The disorder is now being observed in Taiwan, Saudi Arabia, and Kuwait but not in the USSR, Australia, or Africa.

Clinical Features

Mucosa

Orogenital ulceration is so frequent that it provides a keystone to the diagnosis. Buccal ulcers seem insignificantly small and shallow, but they are very painful. They may be found on the lips, gum, tongue, palate, and posterior pharynx. Ulcerative hemorrhagic lesions may also occur in the stomach, intestine, and anus, mimicking peptic ulceration, colitis, or Crohn's regional enteritis. Genital ulcers are more florid than mouth ulcers; they are understandably the source of extreme discomfort and anxiety to the patient (Table 1).

Ophthalmic System

Ocular inflammation is usually bilateral and occurs more frequently in men. There are three ocular presentations: pain and photophobia due to anterior uveitis; blurring of vision due to floating vitreous opacities; and visual failure due to severe retinal vasculitis. There may be vitreous and retinal hemorrhage and exudates, retinal vein and artery occlusion, retinal and optic atrophy, perivascular sheathing, and capil-

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ABBREVIATIONS USED IN TEXT

HLA = human leukocyte antigen
Ig = immunoglobulin

lary closure. Fluorescein angiography has added a fresh dimension to diagnosing and treating leaking retinal vasculitis, which is one of the most troublesome causes of morbidity.[5,6] Hypopyon carries a grave prognosis, for it seems to herald optic atrophy, which ensued within a few months in half of the patients with hypopyon in Istanbul.[7] Less troublesome are conjunctivitis and episcleritis.

Neurologic System

We noted neurologic involvement in 7 of 25 (28%) patients; 6 patients had brain-stem and high cervical cord disease and 1 had a third nerve palsy.[8] One patient had unilateral hearing loss due to vasculitis of the cochlea.

Neuro-Behçet's was noted in 10% of cases in a large Japanese series; it was three times more frequent in men.[9] These patients presented with central motor paresis, brain-stem and cerebellar symptoms, and diverse psychiatric features. The clinical course was an acute onset with subsequent exacerbation and remissions, or a chronic progressive course from the start. Cerebrospinal fluid specimens showed slight or moderate pleocytosis, an increase in the total protein, and particularly an increase in immunoglobulin (Ig) G or IgA levels. Necropsy studies showed perivascular infiltration of mononuclear cells, scattered necrotic or softened foci, and demyelination in the brain stem and around the basal ganglia.

Skin

Erythema nodosum is a frequent clinical feature, appearing on the legs and ankles but also on the neck, face, and buttocks. Erythema nodosum due to any cause is more common in women, except in Behçet's disease, when it predominates in men. If a man presents with erythema nodosum and, say, phlebitis or uveitis or thrombophlebitis, one should inquire immediately whether he suffers from recurrent orogenital ulceration.

Other skin lesions include orogenital ulceration, maculopapular rashes, blisters, sterile pustules, and pyoderma. Dermatographism is frequently elicited, even more commonly than needle-prick sensitivity.

Joints

Recurrent seronegative arthritis is noted in about 60% of patients with Behçet's disease. It usually affects the knees, ankles, and wrists. It is nondestructive and consists of an acute inflammatory reaction around venules with immunoglobulin or immune complex deposition in the walls of veins and capillaries in the superficial layer of the synovial membrane.

The term "MAGIC" was coined to embrace mouth and genital ulcers with inflamed cartilage, features noted in both Behçet's disease and in relapsing polychondritis, which may be regarded as an overlap syndrome because it may occasionally coexist with Behçet's in the same patient.[10] Chondritis is described as painful, edematous aural and nasal cartilage, tracheal and costochondral cartilage, resulting in saddle-nose deformity, deformed pinnae, and inspiratory stridor. There is evidence suggesting an autoimmune phenomenon involving autoantibodies against elastin, type 2 collagen, and proteoglycans.

Cardiovascular System

Cardiovascular involvement occurs in from 7% to 29% of patients, and as many as 20% of those with prominent vas-

TABLE 1.—*Modes of Presentation of Behçet's Disease to Various Disciplines*

Ophthalmology	*Dermatology*	*Neurology*
Iritis	Erythema nodosum	Meningoencephalitis
Hypopyon	Orogenital ulcers	Cranial nerve palsy
Conjunctivitis	Papules	Brain-stem ataxia
Episcleritis	Pustules	Confusion
Retinal vasculitis	Pyoderma	Dementia
Disc edema	Dermatographism	Cerebral thrombophlebitis
Optic neuropathy		Minor strokes
Branch retinal vein occlusion		
Gastroenterology	*Rheumatology*	*Gynecology or Venereology*
Oral, intestinal, and anal ulcers	Synovitis	Genital ulcers
Budd-Chiari syndrome	Chondritis	
Colitis	Seronegative polyarthritis	
Splenomegaly		
Proctitis		
Chest Medicine	*Immunology or Hematology*	*Cardiology*
Hemoptysis	Skin-prick test	Arterial aneurysm
Hemorrhage	Hypersensitivity	Thrombophlebitis
Embolism	Deficiency of C2	Deep vein thrombosis
Pleural effusion	Cryoglobulinemia	Pericarditis/effusion
Pulmonary artery aneurysm	C-Reactive protein and C9 levels increased	Arterial occlusion
Superior vena cava obstruction	ESR raised	Pulseless disease
	Cryoglobulins	Renal artery stenosis
	HLA-B5, -B12, -B27, and -B51	Hemiplegia
		Necrosis of femoral head
		Intermittent claudication

ESR = erythrocytic sedimentation rate

cular involvement die of this complication.[11,12] Venous lesions, ranging from recurrent superficial thrombophlebitis to occlusion of the superior and inferior venae cavae, are more common than arterial occlusions and arterial aneurysm formation, which account for most of the deaths from vascular involvement. Arterial occlusion gives rise to diverse clinical presentations: pulseless disease due to subclavian artery occlusion, hypertension from renal artery stenosis, hemiplegia from carotid artery block, avascular necrosis of the femoral head due to femoral artery stenosis, and, of course, intermittent claudication. Spontaneous arterial aneurysm formation is relatively common both in the aorta and major branches as well as in the smaller peripheral arteries, but most interesting is the peculiar propensity of aneurysms to develop in these patients after arterial puncture. Puncture of arteries for angiography, cardiopulmonary bypass, or surgical bypass of an aneurysm may lead to formation of further false aneurysms at the site of vascular interference or anastomosis. The underlying pathologic process is thought to be a vasculitis that affects the vasa vasorum. Resected vascular specimens have been shown to have fragmentation and splitting of the elastic fibers in the media with a perivascular mononuclear cell infiltration. Necropsy studies have shown widespread myocardial fiber degeneration with mononuclear cell infiltration and endocarditis of the mitral and aortic valves, with replacement of the cusps by granular debris and pleomorphic mononuclear inflammatory infiltrate.

Recurrent superficial thrombophlebitis is commonplace, and thrombosis of the major veins is twice as frequent as arterial involvement, affecting, in order of frequency, the superior and inferior venae cavae and femoral, subclavian, common iliac, hepatic, and great saphenous veins. These venous blocks give rise to exotic clinical pictures such as the Budd-Chiari syndrome and caput medusae.

Alimentary Tract

Gastrointestinal involvement is either infrequent or underdiagnosed. Ulcerations may be found very frequently in the mouth but less often in the stomach and intestine. Colitis mimics Crohn's regional enteritis (Table 2).[13] It is characterized by multiple ulcers of diverse size, appearance, and depth of penetration involving any portion of the large bowel, occasionally with coexisting ileal or anal disease.

Pulmonary System

Intrathoracic involvement is comparatively rare. Patients may present with hemoptysis due to a pulmonary embolism or pulmonary artery aneurysms, recurrent pneumonia due to the underlying vasculitis, pleural effusion, pulmonary fibrosis and obstructive lung disease, pulmonary hypertension, and superior and inferior vena caval obstruction.

Diagnosis

There is no diagnostic laboratory test for Behçet's disease; it is a "bedside" diagnosis based on the multisystem clinical features. To distinguish it from many other multisystem disorders, we devised a points scoring system that has proved to be remarkably selective and definitive (Table 3).[5] A confident diagnosis is only acceptable when the clinical features amount to at least 14 points. No other multisystem disorder commands this number of points with the clinical features outlined in Table 3. Perhaps this scoring system could be changed so that marks are given for being from endemic areas or points allowed for the HLA profile or other laboratory results, but the scoring system shown is based on a decade of experience in the differential diagnosis of numerous multisystem disorders. Although several mimic it, no disorder other than Behçet's disease scores 14 or more points (Table 4).

Laboratory Tests

An acute attack may be marked by a high erythrocyte sedimentation rate, acute-phase proteins, particularly α_2 globulins, high levels of circulating immune complexes, and dramatic alterations in serum complement levels. Serum concentrations of C9 and complement-reactive protein are increased in all forms of the disease, but the serum lysozyme and α_1-acid glycoprotein levels are increased only when there is ocular disease. Circulating autoantibodies are present but only weakly positive in about a third of patients.

TABLE 2.—*Comparison of Intestinal Involvement in Behçet's Disease and Crohn's Disease*

Features	*Behçet's Disease*	*Crohn's Disease*
Nationality	Asian or European	Any
Mouth ulcers	Almost always	Common
Genital ulcers	Frequent	Common
Ocular	Generalized uveitis Hypopyon	Anterior uveitis If HLA-B27 is present
Cardiac involvement	Yes	No
Neurologic involvement	Yes	No
Arthritis	Common	Yes, if HLA-B27 is present
Dermatographism	Yes, frequent	No
Erythema nodosum	Frequent	Rare
Granulomas	Uncommon	Common
Vasculitis	Lymphocytic	Granulomatous
Ileum involved	Occasional	Frequent
Transmural lymphoid aggregates	Infrequent	Frequent
Perforation	Infrequent	Rare
Obstruction	No	Yes
Treatment	Steroids Azathioprine Colchicine Cyclosporine	Sulfasalazine (Salazopyrine [United Kingdom])

Immunopathology

The common denominator of the diverse manifestations of Behçet's disease is a generalized vasculitis. There is infiltration of vessel walls by mononuclear cells and later by polymorphonuclear cells, with increased permeability of the vessel wall and abnormalities in platelet function. Increased platelet aggregations may be correlated with clinically detectable inflammatory activity of the disease. There is also increased plasma viscosity, decreased fibrinolysis, increased plasma levels of prostaglandin E and F_2, and the presence of a serum factor that enhances migration of polymorphonuclear leukocytes—which may be responsible for the frequently seen pustular vasculitis. The terrain or soil of Behçet sufferers is the HLA-B51 and HLA-DRw52 loci, a decrease in the OK T4:T8 ratio,[14] and an increase in NK cells. As a result of gene mapping, what we regard as the terrain this year will be referred to as a specific gene expression in the next year or so.

About a third of these patients have circulating immune complexes; severe retinal disease is associated with the absence of immune complexes, whereas raised levels occur with less severe ocular inflammation and with remission.

TABLE 3.—*Scoring System for the Clinical Diagnosis of Behçet's Disease*

Clinical Features	*Points**
Oral ulceration	4
Genital ulceration	4
Ocular inflammation	4
Retinal vasculitis	2
Erythema nodosum	2
Joint involvement	2
Central nervous system disorders	2
Cardiovascular disorders	2
Gastrointestinal involvement	2
Kidney disease	1
Lung disease	1
Dermatographism	1
Confident diagnosis	>14

*See text for explanation of scoring system.

TABLE 4.—*Disorders That Mimic Behçet's Disease*

Clinical Features	*Differential Diagnosis*
Erythema nodosum and uveitis	Sarcoidosis
Polyarthritis	Seronegative arthritis
Neurologic involvement	Multiple sclerosis
	Encephalitis
Gastrointestinal disorders	Crohn's disease
	Ulcerative colitis
Mucocutaneous ulceration	Reiter's syndrome
	Stevens-Johnson syndrome

TABLE 5.—*Treatment Regimens*

Drug	*Manifestation*
Oral prednisolone	Uveitis
Subconjunctival	Anterior
Eye drops	Anterior
Retro-orbital	Posterior
Plus cyclosporine	Generalized
Azathioprine	Acute symptoms
Chlorambucil	Steroid-sparing
Colchicine	Ocular inflammation
	Skin lesions
	Polyarthritis
Indomethacin	Polyarthritis
Levamisole hydrochloride	Orogenital ulceration
Colchicine	
Thalidomide	
Intravenous epoprostenol (prostacyclin)	Thrombophlebitis
Stanozolol	Decreased fibrinolysis
Atropine sulfate	Anterior uveitis
Eye drops	

Etiology

The cause(s) remain unknown. Herpes simplex might be the triggering antigen, for there is hyperactivity of a T8 suppressor-cytotoxic subset of cells to herpesvirus type I and possibly other microbial antigens.[15,16] There is a constellation of cofactors that includes HLA affinities, ethnicity, T-cell and autonomic imbalance, circulating immune complexes, autoimmunity, blood viscosity, decreased fibrinolysis, sex hormones, zinc deficiency, and polymorphonuclear leukocyte chemotaxis.

Treatment

There are many different treatments—indicating that none is really satisfactory. Corticosteroid therapy is the mainstay, accompanied by either azathioprine, chlorambucil, cyclophosphamide, cyclosporine, colchicine, levamisole hydrochloride, thalidomide, radiotherapy, plasmapheresis, fibrinolytic therapy with stanozolol, and drugs to prevent platelet aggregation (Table 5). Colchicine, levamisole, and thalidomide overcome the orogenital ulceration, but nobody needs to be reminded of the 1961 thalidomide disaster.

The most compelling indication for treatment is to prevent loss of vision, and in this respect using cyclosporine is effective but at the price of troublesome nephrotoxicity.[17]

We commence treating an acute attack with a combination of prednisolone and azathioprine. An unsatisfactory response or relapses indicate combining prednisolone with colchicine and also cyclosporine or chlorambucil. Early vigorous treatment may prevent irreversible visual failure.

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Medical Practice Opinion

EDITOR'S NOTE: *From time to time medical practice questions from organizations with a legitimate interest in the information are referred to the Scientific Board by the Quality Care Review Commission of the California Medical Association. The opinions offered are based on training, experience and literature reviewed by specialists. These opinions are, however, informational only and should not be interpreted as directives, instructions, or policy statements.*

Epikeratophakia in Children

QUESTION:

Is epikeratophakia, a form of refractive surgery that alters the anterior surface of the cornea with a preground donor tissue lens, accepted medical practice for the treatment of aphakia in children?

OPINION:

In the opinion of the Scientific Advisory Panel on Ophthalmology, epikeratophakia is gaining increasing acceptance as one alternative for the optical correction of aphakia in children following cataract removal. In epikeratophakia, the anterior surface of the cornea is altered by adding a machine-lathed donor tissue lens. Because it is a form of lamellar keratoplasty, the refractive error can be changed without intraocular surgery.

Research and experience to date indicate that this procedure may offer a potentially useful alternative to the difficult problem of restoring vision in children with traumatic cataract in the amblyogenic age. However, the results are still not well defined. Further refinements are necessary before full accuracy and stability can be obtained. It is difficult to analyze the results of this technique because it continues to evolve and there is lack of long-term follow-up. Obviously, further longitudinal studies are necessary.

Based on the above and on recent data published by a nationwide study on epikeratophakia for aphakia in children, epikeratophakia should be considered accepted practice for the treatment of aphakia in children in whom there is a documented failure to fit contact lenses and who are older than six months.

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This opinion has been prepared by the CMA Scientific Advisory Panel on Ophthalmology based on available information. It is only an advisory opinion and should not be construed as binding on any individual or as expressing an absolute standard of medical practice. Medical opinion may vary regarding the appropriateness of a particular treatment or service in a given situation. Differences in an individual case should be reviewed by physician medical advisors. Differences of opinion between a medical advisor and attending physician should be referred to the county medical society where the physician practices.

Editorial Comment

Behçet's Disease—Provocative Clues

RALPH SNYDERMAN, MD, *South San Francisco, California*

The fact that this journal has elected to publish an article entitled "Silk Route Disease," as well as this editorial attests to the considerable interest that Behçet's disease evokes in American physicians. Nonetheless, I suspect most physicians reading these articles have only rarely if ever encountered patients with this problem. The initial association of orogenital ulcerations and ocular inflammation, along with systemic inflammatory sequelae and coagulation disturbances, provides a challenge for any unifying etiologic hypothesis. The association of inflammatory eye disease with orogenital ulcerations is attributed to Hippocrates. The modern description of this condition bears the name of Hulusi Behçet, who proposed that recurrent intraocular inflammatory disease in combination with oral and genital ulcers should be considered a distinct disorder.[1]

Clinically, Behçet's disease can present in various ways.[2] Recurrent oral aphthous ulcers are virtually always present (99%) and in roughly 75% of patients these are the initial symptoms. The aphthae are clinically indistinguishable from aphthous stomatitis. They are painful, a distinction from those of Reiter's syndrome, and occur singly or multiply on the lingual, gingival, buccal, or labial mucosa. Behçet's ulcers are rarely confluent, and the observation of ulcers occurring on the palate, pharynx, or tonsils should suggest other conditions such as Stevens-Johnson syndrome or oral pemphigus. The aphthae of Behçet's disease usually last a week to ten days and generally heal without scarring. Ulcers on the scrotum, vulva, penis, or perianal areas may or may not be painful. In women, lesions of the genital mucosa are frequently painless.

As noted in the James article, cutaneous involvement is quite common in Behçet's disease. Frequently, painful recurrent lesions of erythema nodosum appear in crops over the tibia. Superficial thrombophlebitis may occur in the upper as well as lower extremities. Indeed, superficial thrombophlebitis of the upper extremities in the absence of an obvious cause—intravenous injections, for example—should always suggest an underlying systemic disease such as occult carcinoma or Behçet's disease. Acne vulgaris on the upper thorax or face is not uncommon. The phenomenon of pathergy is occasionally observed in Behçet's patients. In such persons, pustules develop on sites of trauma or injections. Pathergy appears to be indicative of hyperactivity of the acute inflammatory response. This phenomenon is also seen in some patients with inflammatory bowel or rheumatic diseases.

Inflammatory eye disease is present in approximately 90% of patients with Behçet's disease and may consist of anterior or posterior uveitis. The initial symptom of anterior uveitis is generally hazy vision due to inflammatory exudation in the anterior chamber fluid. This may lead to the formation of a hypopyon—pus in the anterior chamber of the eye. As noted in the James article, hypopyon is a poor prognostic sign in Turkey, but in the United States, it is unusual for patients to have this problem, since they are generally treated earlier. In the US, anterior uveitis usually does not lead to blindness. In contrast, posterior uveitis is an ominous manifestation of Behçet's disease that frequently results in blindness if not treated aggressively. Retinal exudates and bleeding accompany posterior uveitis. It is distinctly unusual for both eyes to be affected equally during any given attack, although in untreated persons bilateral blindness may occur.

The articular manifestations of Behçet's disease consist of arthralgias and an acute arthritis that accompanies flare-ups elsewhere. Permanent joint damage is rare and the synovial effusion demonstrates an acute inflammatory reaction, but unlike rheumatoid arthritis, complement levels in the synovial fluid are not depressed. Gastrointestinal involvement is generally underrecognized and may be present in almost 50% of patients during acute attacks. Vomiting, abdominal pain, diarrhea, flatulence, and constipation are the most frequent symptoms. More specific to Behçet's are discrete erosions in the terminal ileum or colon or both. These lesions are inflammatory in nature and not as confluent as those seen in ulcerative colitis. In spite of these differences, it may be difficult to distinguish between persons with Behçet's disease who have inflammatory bowel lesions and those with ulcerative colitis or regional enteritis.

Nervous system involvement, while seen in only 10% of patients with Behçet's disease, is a major cause of death in this condition. Central nervous system manifestations include cerebral infarction, cerebellar or brain-stem dysfunction, meningoencephalitis, or cranial nerve palsy. Venous occlusions may be superficial or deep, with the latter potentially leading to death when major vessels such as the inferior or superior vena cava are involved. Occlusive lesions of arteries including the aorta have also been noted.

The treatment of Behçet's disease is discussed in some detail in the accompanying article. In my experience, therapy for posterior uveitis and central nervous system involvement is most important. Chlorambucil has proved to be of substantial benefit to patients with posterior retinal involvement, and doses of 0.1 mg per kg up to a maximum of 0.2 mg per kg per day are suggested. Because pancytopenia is likely to develop with prolonged therapy with chlorambucil, its use should be discontinued as soon as possible. I have found sulfasalazine (up to 4 grams per day) to be useful in some patients, and, considering the relatively low toxicity of this agent, I generally try it in all patients with Behçet's. Cyclosporine may well

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be an additional useful agent for the more severe consequences of Behçet's disease. Treatment of other sequelae should be based on symptoms, with the transient use of corticosteroids providing an important therapeutic approach.

As already indicated, the peculiar multisystem involvement associated with Behçet's and the prevalence of this condition in discrete geographic areas (Silk Route) should provide powerful clues toward the identification of its cause. Despite considerable research on the part of numerous investigators, the cause of Behçet's remains as obscure today as it did in 1937. The leading etiologic candidates are viruses, autoimmunity, or toxic factors. Behçet himself suggested a viral cause for this disease.[1] The isolation of a viral-like agent from the vitreous fluid of a patient was reported in the 1950s,[3] but subsequent studies have yet to identify a particular agent. Indirect evidence for the role of a herpes simplex virus type 1 (HSV-1) has been suggested, and Lehner provided evidence for an HSV-1-specific immunoglobulin (Ig) G_1 subclass circulating immune complex in some patients.[4,5]

Theoretically, many of the pleotropic manifestations of Behçet's disease could be best explained by a neurotropic virus residing primarily in large ganglia such as the trigeminal and pelvic. As also seen with herpes infection, a Behçet's virus infecting such ganglia could account for recurrent ulcerations and inflammatory lesions in mucocutaneous areas involving the eye, mouth, and genital areas. The identification of circulating immune complexes related to viral antigens would go a long way toward explaining the rest of the systemic phenomena. Despite the logic of this argument, the etiologic agent remains to be identified. Evidence for autoimmunity in Behçet's has been provided in that antibodies and lymphocytes from such patients react with mucosal cells.[5] Nonetheless, this reactivity is not specific and occurs in patients with only aphthous ulceration. Evidence for a genetic predisposition has been raised with some surveys identifying HLA-B51 and HLA-DRw52, but, again, the evidence is far from compelling.[4]

Various toxic agents such as heavy metals (zinc) and organophosphate pesticides, and ingestion of certain foods such as walnuts have all been associated with the etiology of Behçet's disease. I share some responsibility for the implication of walnuts in the search for the etiology of this syndrome. My colleagues and I observed a dramatic historical association of walnut ingestion with disease exacerbation in a number of patients with Behçet's disease being treated at the National Institutes of Health.[6] During the course of these studies, we noted that the ingestion of approximately a half cup of English walnuts led to a profound fall of lymphocyte reactivity to T-cell mitogens in normal persons and in patients with Behçet's disease. In the latter, however, walnut ingestion led to exacerbation of symptoms. Unfortunately, this potentially provocative observation has not led to a further understanding of the pathogenesis of the disease. In regard to the suggested role of a neurotropic virus, however, it is fascinating to speculate that transient immunosuppression, which may be due to numerous hormonal, infectious, metabolic, or toxic causes, can lead to a transient alteration in host resistance and consequently reactivation of an otherwise latent virus. This hypothesis, of course, remains to be formally tested.

In the article elsewhere in the journal, the association of Behçet's disease with the silk trade route provides yet another important clue. I would like to suggest that the recent observation that retroviral infections may follow geographic migrations lends additional support for a similar cause in Behçet's disease. For example, it has been suggested that infection by the T-cell lymphotropic virus-1 (HTLV-1) followed the route of Portuguese sailors from Africa to Japan.[7] More recently, the human immunodeficiency virus (HIV) is said to have followed an apparently traceable path from Africa to many other parts of the world. Interestingly, the prevalence of HTLV-1 and Behçet's in Japan is distinctly different, with the latter being far more common in northern islands while the HTLV-1 is prevalent in the southern islands. It is hoped that epidemiologists will be provoked by the term "Silk Route disease" to pay a bit more attention to uncovering common features linking these geographic areas to Behçet's disease.

I suspect this epidemiologic hint, in combination with the recent revolution in biotechnology, has brought near the time when major breakthroughs towards understanding the etiology and pathogenesis of this ancient disease can be made. Although Behçet's disease is not a major problem in the United States, it is a leading cause of blindness in Japan and is very common in the Middle East. I hope, therefore, that the readership of this journal will be provoked into thinking further about this most fascinating and perplexing disease.

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Specialty Conference

Medical Risks of Cocaine Use

Discussant
CAROL KURTZ BATES, MD, *Portland*

This discussion was selected from the weekly Grand Rounds in the Department of Medicine, Oregon Health Sciences University School of Medicine, Portland. Taken from a transcription, it has been edited by George A. Porter, MD, Professor and Chair, Department of Medicine.

Cocaine abuse can lead to a life-threatening illness. When patients present for treatment of its complications, they rarely volunteer information concerning their personal use of cocaine. Excited delirium is often the first stage of one of the life-threatening complications that may include myocardial infarction, subarachnoid hemorrhage, and intestinal ischemia or infarction. Two other presentations in which cocaine abuse should be considered are spontaneous abortion and pneumomediastinum. While the incidence of such adverse outcomes is unknown, these complications represent unique risks for the growing number of cocaine abusers.

CAROL KURTZ BATES, MD*: Reports of illness associated with cocaine use have been prominent in both the medical and lay literature. In June 1986 national media attention focused on the issue of sudden death in cocaine users when two prominent, healthy athletes died of presumed cocaine toxicity. A variety of nonfatal pathophysiologic events have also been attributed to cocaine use. In particular, a number of reports of premature cardiac events have appeared in medical journals in recent years. In this discussion, I will review the data linking cocaine use with a number of reported consequences, including sudden death, cardiac toxicity, pulmonary effects, and adverse outcomes in pregnancy.

Sudden Death and Cocaine Use

Sudden death has been reported in several different settings of cocaine abuse. Len Bias, a basketball player and one of the above-mentioned athletes, was said to be a first-time user. Chronic abusers have also died from cocaine reactions, sometimes without a known change in their dose of use. The syndrome has also been clearly described in "body packers" who ingest large quantities of wrapped cocaine for the purpose of smuggling.[1]

The magnitude of the problem has not been well defined. Data from two representative series follow. During a two-year period in Los Angeles County, 20 deaths were ascribed to cocaine; in 18 of those, cocaine was the only illicit substance identified.[1] A larger series was reported from Dade County in Florida, where 60 deaths were attributed to cocaine over four years.[2] Of these deaths, 92% were thought to be accidental.

Data with respect to what represents a lethal dose of cocaine in humans remain murky at best. First, historical data quantitating doses of drugs in recreational settings are often unavailable or unreliable. Much of the data is, therefore, pieced together from postmortem blood levels, which have varied widely.[1-3] This information is further confounded in that cocaine probably continues to be metabolized after death. Metabolites of cocaine have rarely been measured.[2,3] Animal studies have not been very helpful in defining the lethal dose of cocaine because of substantial variation among species. A rough summary of available animal data would point to a lethal dose of about 100 mg per kg. For comparison, the often-quoted "safe" dose for local anesthesia is 200 mg. Fatalities, however, have been reported with doses of cocaine as low as 25 mg. The average fatal dose in humans is said to be 1.4 gm.[4]

When death occurs, it may be the end result of a rapid progression through a phenomenon that has been termed the "cocaine reaction." This has been described mainly by physicians at the Haight-Ashbury Clinic in San Francisco and has also been called the "Casey Jones" reaction.[5] Patients with cocaine toxicity are said to progress through several stages.

Most patients will have mild toxicity and will not progress beyond stage one. Findings include many behavioral changes: restlessness, pressured speech, and teeth grinding. Examination reveals tachycardia, hypertension, tachypnea, and hyperthermia. Pupils are dilated but reactive. Patients are often tremulous, diaphoretic, and pale.

When patients progress to the stage of advanced stimulation, they are usually unresponsive to stimuli, hyperreflexic, and may have seizures and ventricular arrhythmias. If untreated, they may die. A similar sequence of events has been observed in the dog model for cocaine overdose. Progression through these stages may occur within a few minutes to a few hours.

An interesting variant of the cocaine reaction was described by a group in Miami.[6] They observed seven fatalities preceded by an "excited delirium." Police were called to restrain patients who were often shouting, thrashing, and otherwise physically violent. These patients progressed to cardiopulmonary arrest on the scene or during transport in police custody.

Observations made in body packers have also helped to define the syndrome of acute cocaine toxicity. As mentioned previously, body packers, or "mules," ingest many packets of

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Reprints are not available.

wrapped cocaine for transport. Packets are swallowed or are inserted in the rectum or vagina.

These persons have almost always returned very recently from South America. It is thought that this is currently a common method of importing cocaine and that most smugglers survive the experience. Toxicity only occurs when the packages rupture or leak through a semipermeable membrane. When toxicity occurs, symptoms match those noted earlier, including hypertension, tachycardia, hyperthermia, mydriasis responsive to light, and seizures.[7,8]

Suspicion of body packing can be confirmed with an abdominal x-ray film. Multiple well-defined densities in the stomach, small bowel, and colon are seen.[9,10] Densities in the stomach and ascending colon are more easily distinguished from stool. Occasionally, one may see an oblong density with a rosette at one end. The so-called double condom sign is one in which a crescent of air surrounding an ovoid density is seen. It is thought that air trapped in the layers of wrapping produces this phenomenon.

Body packers who do not show signs of cocaine toxicity can be managed conservatively. A series of 50 patients from a jail ward in Florida were followed medically.[10] There were 54 to 182 packets seen per patient. On the average, these patients took 28 hours to pass all of their packets. Once they began to pass packets per rectum, they were treated with mineral oil. Evacuated packets were carefully examined for evidence of wrapper deterioration. When abdominal x-ray films confirmed elimination of all packets, the patients were discharged. Operations were performed for signs of obstruction, cocaine toxicity, or any evidence of packet decay. In this series, a total of 9 patients required operation, and there were no deaths.

For patients who show signs of cocaine toxicity from body packing or other routes of ingestion, management is as outlined in Table 1. Obviously, if the patient has respiratory or cardiac arrest, airway protection and cardiopulmonary resuscitation are indicated. Because of the frequency of hyperthermia in these patients, it is important to follow the core temperature.

Diazepam is the recommended therapy for agitation and other behavioral manifestations of toxicity.[5,11] Interestingly, hypertension, tachycardia, and other signs of catechol excess have been reported to respond to diazepam. Although it has not been used extensively in humans, chlorpromazine pretreatment in the dog model prevents the cardiovascular manifestations of toxicity as well as hyperthermia, acidosis, and death.[12] Propranolol has been used clinically, but in the experimental setting it does not prevent death.[12,13] There is one report in the literature of propranolol-induced hypertension during treatment of cocaine intoxication.[14] It is speculated that propranolol may block both β_1 and β_2 receptors, leaving unopposed α-adrenergic receptor stimulation. It may, therefore, be preferable to use a β_1 selective agent or a combined alpha-beta blocker, although there is little reported experience with this. Finally, calcium channel blockers may also have a role in treating cocaine toxicity. In a study using dogs, pretreatment with nitrendipine substantially increased survival time and the size required for a dose to be lethal.[15]

In summary, patients who present with agitated delirium or signs of catechol excess should be monitored, given the risk of their progressing to arrhythmias and seizures. Treatment modalities most commonly used include diazepam and beta blockade, although chlorpromazine and calcium channel blockers may also be effective. The risk of sudden death in cocaine use, however, is not well defined.

TABLE 1.—*Management of Cocaine Reaction*

1. ABCs—airway, cardiopulmonary resuscitation
2. Follow core temperature
3. Diazepam 2.5 to 5 mg IV q 5 min as needed
4. ? beta-blocker for hypertension or ectopy
5. ? calcium-channel blockers
6. ? chlorpromazine

Cardiac Toxicity

A 1986 report of seven patients with presumed cardiac toxicity[16] was only one of many detailing cocaine use and cardiac toxicity. Reported cardiac events attributed to cocaine use include myocardial infarction,[16-28] arrhythmias,[16,29-31] aortic rupture,[32] and myocarditis.[16,24] Myocardial infarction has been the most frequently reported event. Table 2 provides data on the 23 reported cases of myocardial infarction associated with cocaine use. A number of points can be made. First, the age range of reported cases is 19 to 44 years. The mode of ingestion of the drug was quite variable, but more than a half used cocaine intranasally. Many of these patients had confounding risk factors for coronary disease; over 50% were smokers. A number of the patients abused other substances, including heroin and marijuana. Finally, most had obstructive coronary artery disease when studied with angiograms. Of note, however, is that eight patients had normal coronary arteries; four of these eight were studied with ergonovine challenge, which produced negative results in all patients.

There are a number of obvious problems with these data. First, this is retrospective information. No one has studied these patients with cocaine challenge in the cardiac catheterization laboratory. Second, the coronary anatomy of this group of patients was heterogeneous. In a few patients, anatomy was unknown. Of more concern is that the temporal relationship between cocaine use and infarction varied widely. Some patients were said to develop pain immediately, but in one patient, pain occurred more than 24 hours after use but was still attributed to cocaine. Finally, it is possible that other abused substances played a role in the results with some of these patients.

A number of mechanisms may account for cocaine-induced ischemia.[33,34] Cocaine clearly can increase myocardial oxygen demand given the common findings of hypertension and tachycardia. Oxygen demand may also increase because of increased contractility. Moreover, cocaine is commonly cut with a number of substances, including amphetamines, which are well documented as increasing myocardial oxygen demand. It has been postulated that cocaine increases the tendency for thrombosis, but there is no experimental support for this idea. Another potential mechanism is that of vasospasm either via a direct effect of cocaine or via sympathetic potentiation. If this is indeed the mechanism, ergonovine is unlikely to help in the clinical setting given the history of negative studies in this population. Finally, both coronary emboli and coronary vasculitis could be potential mechanisms, but there has been no evidence for these phenomena clinically or pathologically.

It is not possible to unequivocally state that cocaine abuse causes myocardial infarction. The association appears to be a strong one, however, and a number of observations can be

made. First, the association appears to be independent of the route of ingestion. Second, the time of onset of ischemia following cocaine use is unknown. Third, cardiac toxicity is not clearly dose-related. In patients with obstructive coronary artery disease, cocaine probably can induce ischemia or infarction because of the increase in myocardial oxygen demand. In a young patient with ischemia or infarction, one should have a heightened suspicion of cocaine use given the number of case reports. Finally, as is true of the data on sudden death in cocaine users, the incidence of myocardial infarction or ischemia is totally unknown.

There are other types of cardiac toxicity that have been attributed to cocaine use. Supraventricular arrhythmias have been seen.[31] Several patients have been reported to have ventricular tachycardia or fibrillation unassociated with myocardial infarction but temporally related to cocaine use.[16,29,30] Only one reported patient was studied extensively.[16] He had ventricular tachycardia followed by fibrillation after snorting approximately 500 mg of cocaine. Cardiac catheterization, ergonovine stimulation, and electrophysiologic studies were all normal in this patient, suggesting that he had no underlying cardiac disease.

Reviews of the medical consequences of cocaine use commonly mention aortic rupture as a complication. In fact, there is only one report of this in the literature: A 45-year-old free-base user had a ruptured aorta at autopsy, probably because of hypertension associated with cocaine ingestion.[32]

Cardiomyopathy has also been reported in this setting. Several patients, not surprisingly, have had a fall in ejection fraction following myocardial infarction.[26,27] There are also reports of a syndrome in cocaine users similar to postviral myocarditis. One patient had biopsy-proved myocarditis that responded to therapy with prednisone and azathioprine.[16] Another report is based on autopsy findings in a 21-year-old with sudden death following cocaine use. He had a documented anterior myocardial infarction but also had lymphocytic myocarditis.[24] Reportedly, the autopsy on Len Bias showed tiny foci of lymphocytes and macrophages infiltrating myocardium.[35] These case reports have led some investigators to suggest the concept of a cocaine-induced toxic cardiomyopathy.[27] Although this may be true, these patients instead may have had viral or idiopathic myocarditis incidental to cocaine use.

There are a number of other vascular events that have been attributed to cocaine. There have been two case reports of intestinal ischemia associated with cocaine use.[36] Literature on cerebrovascular events is more extensive. There are four reported cases of subarachnoid hemorrhage in cocaine users.[37-39] One of these patients had an aneurysm of the anterior communicating artery and another had a posterior communicating aneurysm. A third had an arteriovenous malformation. There are two reported cases of parenchymal central nervous system hemorrhage[38,40] and two cases of bland infarction.[38,41] Once again, the mechanism of hemorrhage is thought to be a sudden rise in blood pressure causing the rupture of a preexisting lesion. Those who have seen these patients warn that headache associated with cocaine use may be a symptom of an unsuspected aneurysm or arteriovenous malformation.[33]

Pulmonary Effects

As mentioned previously, vascular toxicity is independent of the route of ingestion of cocaine. In contrast, most forms of pulmonary toxicity are associated with a single route of ingestion. In particular, free-basing appears to have a number of adverse effects on the lungs.

TABLE 2.—*Myocardial Infarctions Attributed to Cocaine*

Reference	*Age/Sex*	*Route*	*Dose*	*Temporal Relation*	*Infarct Location*	*Coronary Anatomy*	*Smoking*	*Other Drugs*
Coleman et al[17]	38/♂*	Intranasal	0.5 g	?	Anterolateral	?	Yes	...
Kossowsky and Lyon[18]	27/♂*	Intravenous	?	?	Anterior	?	...	Heroin
	30/♂	Intravenous	?	?	Anterolateral	100% LAD	Yes	Heroin/alcohol
	35/♂	?	?	?	Anterior	90% LAD	...	...
	36/♂	Intravenous	?	?	Anterior	75% LC	...	Heroin
	43/♂	Intranasal	?	'Soon after'	Inferior	100% RCA	...	...
	44/♂	Intranasal	'6 lines'	'Shortly after'	Inferoposterior	?	Yes	...
Schachne et al[19]	21/♂	'Inhaled'	0.25 g	5 h	Inferior	Normal	...	...
Pasternack et al[20]	35/♂	Intranasal	?	?	Anterior	LAD, LC, RCA stenoses	Yes	...
	37/♂	Intranasal	?	?	Anterior	LAD stenosis	Yes	...
	38/♂	?	?	?	Anterior	LAD stenosis	Yes	...
Howard et al[21]	28/♀	Intranasal	1.5 g	5 h	Anterior	Normal †	...	...
Cregler and Mark[22]	38/♂*	Intranasal	?	45 min	Inferior	Normal †	Yes	Heroin/alcohol
Gould et al[23]	32/♂	Cocaine/tobacco cigarette	?	1 h	Anterolateral	...	Yes	...
Simpson and Edwards[24]	21/♂	Intravenous	?	30 min	Anterior	LM, LAD thrombus	Yes	Marijuana/ alcohol
Weiss[25]	19/♂*	Intranasal	?	'Just prior'	Inferior	60% RCA, 40% LAD	Yes	...
Rollingher et al[26]	42/♂	Intravenous	?	2 h	Anterior	Normal	Yes	Alcohol
Weiner et al[27]	42/♂*	Intranasal/IV	?	> 24 h	Anterior	Normal	Yes	Heroin/alcohol
Wilkins et al[28]	33/♂	Intranasal	2.0 g	'After an evening'	Anterior	Normal	...	...
Isner et al[16]	29/♂	Intranasal	1.0 g	1 h	Inferior	?	Yes	...
	28/♀	Intranasal	?	6 h	Anterolateral	Normal †	...	...
	37/♂	Intranasal	?	?	Anterior	100% LAD	...	...
	23/♂	Intranasal	?	11 h	Inferior	Normal †	...	...

LAO=left anterior descending, LC=left chamber, RCA=right coronary artery, LM=left main

*These patients had recurrent infarctions.
†Ergonovine stimulation during cardiac catheterization induced no spasm.

A group in Chicago did pulmonary function testing in 19 free-base users.[42] The only significant abnormality found was that of a decrease in diffusing capacity. Total lung capacity and one-second forced expiratory volume were greater than 80% predicted. Ten of 19 patients had a diffusing capacity of less than 70% of predicted. Symptoms of cough and dyspnea were reported in 63% of patients but were more common in those with impaired diffusing capacity. Interestingly, duration of use was not predictive of impairment. Tobacco use and age also did not correlate with impairment.

Free-basing has also been associated with pneumomediastinum.[43-48] There are at least seven reports of patients who developed this after a Valsalva's maneuver or partner-applied positive pressure. Patients may also have pneumopericardium and pneumothorax. Symptoms include pleuritic pain and dyspnea. Examination may elicit Hamman's sign or a mediastinal crunch. The mechanism is thought to be an alveolar rupture with dissection of air to the mediastinum. Treatment is conservative; few patients have required chest tube drainage. The major differential diagnosis in this setting is that of esophageal rupture, which can be ruled out with an esophagogram.

Additional pulmonary complications of cocaine use are impaired diffusing capacity of the lung for carbon monoxide (DLCO), pneumomediastinum, bronchiolitis obliterans, pulmonary edema, and nasal septal perforation and sinusitis. Bronchiolitis obliterans has been reported in two free-basers.[49] Noncardiogenic pulmonary edema has occurred in cocaine users and is not specific for any route of ingestion.[1,2,6,7,50] A number of upper airway problems have been noted with the intranasal use of cocaine. The incidence of nasal septal perforation may have been exaggerated, but it certainly does occur.[1] Cocaine probably causes mucoperichondrial ischemia followed by necrosis.[40,51] Earliest symptoms of a septal defect include whistling on inhalation, nasal crusting, and bleeding. The differential diagnosis of septal defects includes collagen vascular disease, tuberculosis, leprosy, tertiary syphilis, and trauma. Other upper airway problems include sinusitis and osteitis.

Cocaine and Pregnancy

Cocaine use has also been associated with adverse outcomes in pregnancy. In 1985 pregnant women who were cocaine or heroin users or both were studied.[52] The study was not controlled for tobacco, alcohol, or marijuana use. Heroin users were given methadone. Almost all cocaine use was intranasal. The major finding was a higher rate of spontaneous abortion in cocaine users than in those who used heroin or in a control group. Four patients had abruptio placentae, with all episodes of abruption occurring after intravenous cocaine use. Infants born to cocaine users were jittery and had depression of interactive behavior. There was little evidence of teratogenicity in this study. Only one cocaine user had an infant with prune-belly syndrome. Infant growth was not affected.

Abruptio placentae was thought to occur because of maternal hypertension. Spontaneous abortion was thought to be due to placental vasoconstriction and increased uterine contractility. A study on pregnant ewes supports this hypothesis.[53] This study looked at both maternal and fetal hemodynamics. Shortly after cocaine injection, maternal blood pressure increased, uterine vascular resistance increased, and uterine blood flow fell. Fetal oxygenation then fell, while the fetal heart rate increased. Interestingly, when cocaine was injected directly into the fetus, the heart rate and blood pressure increased but oxygenation remained stable. Thus, placental vasoconstriction was confirmed in this model. The observed fetal hypoxia appeared to be due to decreased placental blood flow and was not a direct effect of circulating cocaine in the bloodstream of the fetus.

In summary, both human and animal studies suggest that cocaine use in pregnancy is associated with an increased incidence of abruption and spontaneous abortion. Infant behavior is also abnormal.

TABLE 3.—*Toxicity by Route of Ingestion*

Route	*Result*
Any	Sudden death, cardiac toxicity, subarachnoid hemorrhage, other vascular events, pulmonary edema
Intravenous	Endocarditis, hepatitis, human immunodeficiency virus infection, abscesses
Free base	Cough, sore throat, impaired diffusing capacity, pneumomediastinum
Intranasal	Nasal septal perforation, anosmia, sinusitis, osteitis

Routes of Cocaine Ingestion

Having reviewed cocaine toxicity through a tour of the organ systems, I am going to briefly review toxicity according to routes of ingestion (Table 3). As noted before, sudden death, cardiac toxicity in general, subarachnoid hemorrhage, and other vascular events can occur with any form of cocaine use. The problems peculiar to intravenous abuse have not been stressed because they may occur with intravenous use of any illicit drug. These complications of intravenous drug abuse include endocarditis, hepatitis, human immunodeficiency virus infection, and abscesses. In particular, patients may get pulmonary or intracranial abscesses.[54] Free-base users may complain of cough or sore throat. They may have impaired diffusing capacity or may get pneumomediastinum. Snorting is associated with upper airway lesions such as nasal septal defects, sinusitis, and inability to smell or taste.

When patients present to primary care providers and subspecialists for treatment of complications of cocaine abuse, they may not volunteer information about their habit. A history of cocaine use should be pursued when patients present with an excited delirium, since this can be the first sign of a life-threatening illness. Vascular events such as myocardial infarction, subarachnoid hemorrhage, and intestinal ischemia in young patients are suspect. Pneumomediastinum and spontaneous abortion may also be clues to cocaine use. Nasal septal defects or other upper airway lesions may be presenting complaints. One might look for the "coker's dyad" of a gold coke spoon necklace and a bottle of nasal spray in the pocket.[5]

Educating an asymptomatic patient regarding the risks of cocaine use is a bit more troublesome. Most of the information on adverse effects of cocaine use is in the form of case reports. Although the array of these worrisome reports is impressive, the incidence of such adverse outcomes remains unknown. Assessment of risk to the individual cocaine user is thus impossible to make.

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The Pathogenesis of Acute Left Ventricular Failure
The Role of the Pericardium

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs Homer A. Boushey, Professor of Medicine, and David G. Warnock, Associate Professor of Medicine, under the direction of Dr Lloyd H. Smith, Jr, Professor of Medicine and Associate Dean in the School of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, School of Medicine, San Francisco, CA 94143.

RICHARD K. ROOT, MD*: *Measures of pulmonary capillary wedge pressure are sometimes used as estimates of left ventricular filling pressure and, therefore, as estimates of left ventricular end-diastolic volume. Knowing the filling pressure is only half of the story, however, for end-diastolic volume is determined by the pressure difference across the ventricular wall. The pressure outside the ventricle is, of course, the pericardial pressure, and the importance of the pericardium in acute left ventricular failure is increasingly recognized. Dr Eldon Smith, Professor and Chair of the Department of Medicine at the University of Calgary, will update us on this subject.*

ELDON R. SMITH, MD†: Acute left ventricular failure, characterized by elevated pulmonary venous pressures and excessive transudation of fluid into the alveolar spaces, complicates many cardiovascular disease processes. Although there has been a great improvement in our understanding of the pathophysiology involved—particularly related to the importance of diastolic dysfunction—we remain uncertain as to the exact mechanism(s) in many situations. In this conference, the focus will be on recent experimental and clinical evidence that suggests that the pericardium may play a more central role in the mediation of acute left ventricular failure than was previously thought.

The Clinical Problem

Let us examine the case of a patient with acute anterior wall infarction. A few hours after admission, the patient had a flow-directed catheter inserted and the hemodynamics were measured (Table 1). Of note is the fact that the stroke volume and cardiac output were normal—values indexed to surface area were also normal—although the mean pulmonary capillary wedge pressure was elevated. Traditionally, we have ascribed the elevated filling pressure in this clinical setting to reduced compliance of the infarcted myocardial segment. Experimental evidence, however, suggests that acutely infarcted myocardium is more, rather than less, compliant than normal myocardium[1]; impaired distensibility does develop over days to weeks, presumably secondary to the developing fibrosis. Thus, although diastolic compliance was apparently reduced in this patient, it is not clear that changes in myocardial stiffness were responsible.

The patient subsequently received an infusion of nitroglycerin and after stabilization, the values shown in the right column of Table 1 were determined. There was no significant change in the heart rate, cardiac output, or stroke volume despite a major reduction in the left ventricular filling pressure. Given our traditional concepts of physiology, this is also somewhat difficult to understand. Based on Sarnoff's adaptation of Starling's law of the heart, we might expect that such a major decrease in the left ventricular filling pressure would effect a decrease in left ventricular volume and be associated with a decrease in stroke volume. It is generally recognized, however, that administering nitroglycerin to such patients usually does not result in a major reduction in left ventricular volume. This is well illustrated in Figure 1, taken from the work of Ludbrook and co-workers.[2] Here, nitroglycerin produced a major decrease in diastolic pressure, with only a minimal change in left ventricular volume. Thus, there was a parallel downward shift in the diastolic pressure-volume relation with an apparent improvement in left ventricular compliance in response to the nitroglycerin.

Traditionally, acute alterations in apparent diastolic compliance would be attributed to changes in myocardial relaxation or to altered distensibility. In vitro studies of cardiac muscle, however, have not shown any alteration in these variables in response to nitroglycerin. Major upward displacement in the diastolic pressure-volume relation such as that shown in Figure 1 would be expected to occur primarily in response to processes such as hypertrophy, fibrosis, or infiltration. Acute myocardial ischemia is a possible exception,

TABLE 1.—*Hemodynamics Before and During Nitroglycerin Infusion*

Measured	*Control*	*With Nitroglycerin*
Heart rate, beats/min	96	95
Systolic arterial pressure, mm/mercury	110	105
Right atrial pressure (mean), mm/mercury	8	2
Wedge pressure (mean), mm/mercury	17	10
Stroke volume, ml	64	61
Cardiac output, liters/min	6.2	5.8

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(Smith ER, Tyberg JV: The pathogenesis of acute left ventricular failure—The role of the pericardium [Medical Staff Conference]. West J Med 1988 Apr; 148:445-450)

during which ischemia-induced calcium influx might alter the distensibility of the myocardium.[3] In view of these considerations, it is not surprising that the mechanism of such parallel shifts in the left ventricular pressure-volume relation as illustrated for nitroglycerin has remained controversial.

The Role of External Constraint

One possible explanation for such load-mediated shifts in the left ventricular pressure-volume relation is unappreciated alterations in pericardial pressure.[4] Figure 2 shows a simple model of the two ventricles enclosed in a semirigid pericardium. In **B,** the left ventricular intracavitary pressure is 15 mm of mercury at end-diastole, while pressure in the pericardium is 5 mm of mercury. The left ventricular transmural pressure, therefore, is 10 mm of mercury; this represents the true distending pressure (preload) on the left ventricular myocardium. The effects of dilatation of the right ventricle in this model are illustrated in **A** (Figure 2). This results in more of the (potential) space in the pericardium to be occupied by the right ventricle, with a subsequent increase in pericardial pressure to 15 mm of mercury. For the left ventricular volume to remain the same as in **B,** diastolic pressure must rise to 25 mm of mercury; transmural pressure remains unchanged at 10 mm of mercury.

Given the poorly compliant nature of the pericardium,[5] one can readily appreciate how minor changes in total cardiac volume could effect significant changes in pericardial pressure. Of course, a change in volume of any of the cardiac chambers—not just the ventricles—or an alteration in the amount of pericardial fluid would alter pericardial pressure and, therefore, shift the left ventricular diastolic pressure-volume relation.

Although this model is simple and compelling, a major impediment to its acceptance has been that our conventional understanding of pericardial pressure (in the absence of effusion) is that it is similar to intrathoracic pressure and varies little in response to alterations in cardiac volume. This concept is based primarily on the experimental observations of Kenner and Wood,[6] who showed that pericardial pressure measured with a fluid-filled catheter system varied insignificantly in response to constriction of the aorta and pulmonary artery, interventions that resulted in substantial increases in the right atrial pressure and that presumably increased the total volume of the heart. Whereas these findings have been widely accepted, the possibility exists that the method used to measure pericardial pressure was not appropriate. Of note is the observation that Agostoni and Permutt and colleagues,[7,8] in addressing the subject of pleural pressure, have been careful to distinguish between "liquid pressure" such as might be measured with a fluid-filled catheter system and "surface pressure." It is this latter pressure—actually a compressive contact stress—that is of importance to this discussion.

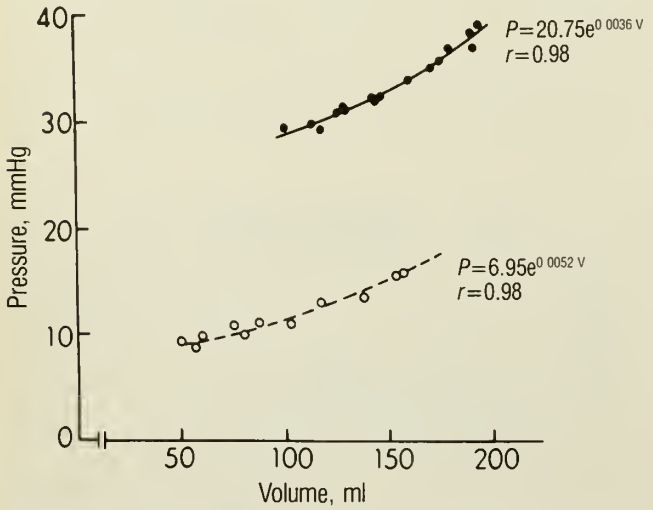

Figure 1.—Diastolic pressure-volume relations before (●) and after (O) nitroglycerin (NG) administration. Volume data points represent consecutive frames from a cine angiogram (based on data from Ludbrook et al[2]).

The Measurement of Pericardial Pressure

As long ago as 1960, Holt and co-workers[5] reported measuring pericardial pressure with a liquid-containing balloon and showed that vascular volume expansion resulted in substantially increased pericardial and intracavitary left ventricular pressure. Using a similar balloon, Smiseth and colleagues[9] working at the University of California, San Francisco, showed significant alteration in pericardial pressure occurring secondary to changes in preload and afterload in a model of left ventricular failure. Thus, these two techniques, a fluid-filled catheter and a liquid-containing balloon, when used to measure pericardial pressure, provide very different results.

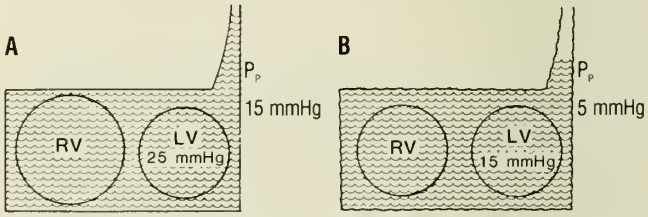

Figure 2.—Schematic model of the ventricles in the pericardium. RV = right ventricle; LV = left ventricle; P_P = pericardial pressure (from Smith et al,[16] with permission).

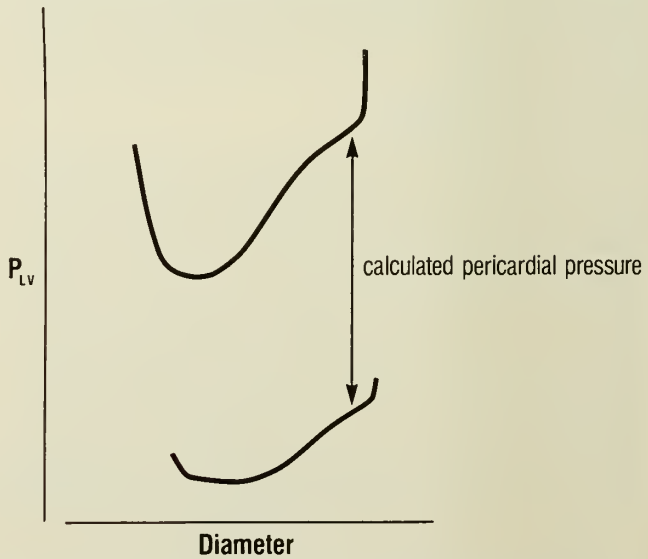

Figure 3.—The diagram shows the "calculated" pericardial pressure concept, with the upper curve representing left ventricular diastolic pressure (P_{LV}) versus diameter with the pericardium intact and the lower curve representing the relationship after the pericardium had been removed, the lungs retracted, and cardiac volume adjusted to be equal at end-diastole to that in the upper curve. The lower curve, therefore, represents transmural pressure (from Smiseth et al,[10] with permission).

To develop a "gold standard" for pericardial pressure to which these two measurement techniques might be compared, we used a simple, static equilibrium concept. At the instant of end-diastole when all movement in the left ventricle has stopped, the blood within the cavity exerts a pressure against the endocardium that must be exactly opposed by the sum of the transmural pressure and the external (pericardial) pressure. This concept is illustrated schematically in Figure 3. Transmural pressure can be directly measured experimentally by opening the chest, removing the pericardium and retracting the lungs so that the external surface of the left ventricle is exposed to atmospheric pressure. Under these circumstances, transmural pressure is equal to intracavitary pressure. Thus, at any given left ventricular end-diastolic volume, the correct pericardial pressure is the pressure that must be added to the transmural pressure to equal left ventricular intracavitary pressure.

Using these concepts, we were able to compare the data from both the fluid-filled catheter and a carefully calibrated liquid-containing balloon to "calculated" pericardial pressure in a series of dogs.[10] The results showed that the liquid-containing balloon transducer correctly reflected pericardial constraint despite the presence or absence of fluid within the pericardial space. Conversely, the fluid-filled catheter system grossly underestimated pericardial pressure when the pericardium was completely empty of fluid and recorded the same pressures as those recorded by the balloon transducers only when approximately 30 to 40 ml of fluid had been infused into the pericardial space. Even when the pericardium had four or five slits made in the ventral and lateral surfaces, allowing all the fluid to drain, the balloon transducer accurately reflected pericardial pressure, whereas liquid pressure as measured by the fluid-filled catheter fell to zero.

On the basis of these experiments, we concluded that pericardial pressure can be accurately measured by a balloon transducer, whereas the traditional catheter system for measuring intravascular pressure seriously underestimates pericardial constraint unless there is excessive fluid within the pericardial space.

Pericardial Pressure in Humans

Unfortunately, balloon transducers cannot easily be used to measure pericardial pressure in humans. An empiric observation in the animal laboratory, however, was that right-sided filling pressure did not differ significantly from pericardial pressure measured with a balloon transducer.[11] This suggests that right atrial and right ventricular transmural pressures are normally quite low and hardly detectable by noting the difference between right ventricular filling pressure and pericardial pressure.[12] To determine if this relationship held true in humans, we did a study in patients undergoing cardiac surgical procedures.[13] Following thoracotomy in nine patients, a flat, liquid-containing balloon transducer was inserted into the pericardial space over the lateral left

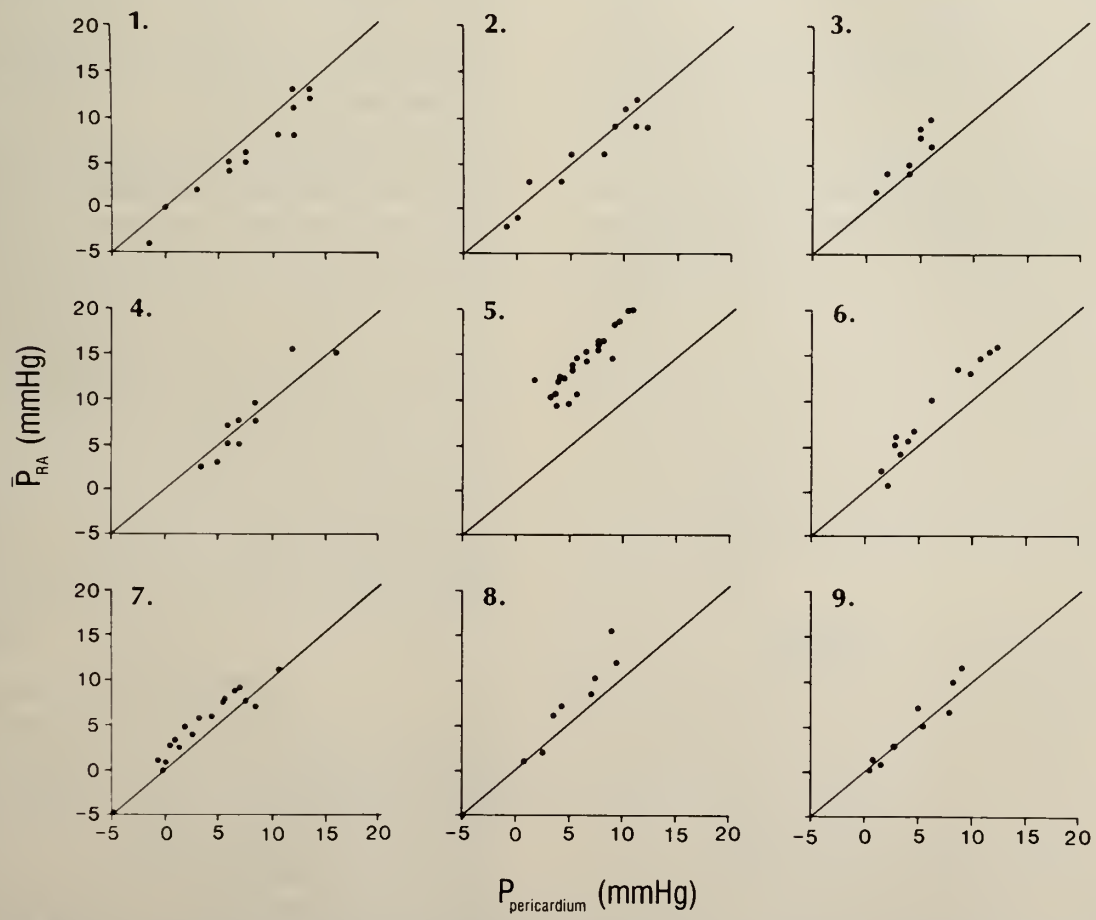

Figure 4.—Individual patient plots of mean right atrial pressure (P_{RA}) on the ordinate *v* pericardial pressure ($P_{pericardium}$) on the abscissa. Pericardial pressure was measured with a liquid-containing balloon transducer. In patient 5, the correlation coefficient was 0.94, although data are shifted upward from the line of identity; this probably reflects an undetected error in baseline (from Tyberg et al,[13] with permission).

ventricular wall through a small transverse incision. Mean right atrial and pericardial surface pressures were then compared over a large range of right atrial pressure effected by intravenous infusion. In each patient there was a close linear relationship (mean $r = 0.94 \pm 0.03$) with slopes not different from unity between mean right atrial and pericardial pressures (Figure 4).

More recently, similar findings have been reported by Boltwood and co-workers.[14] These workers studied 20 patients undergoing cardiac surgery and compared mean diastolic right atrial pressures with pericardial pressures measured with a balloon transducer. In the patient group without cardiac enlargement, there was no difference between right atrial pressures and pericardial surface pressures measured over either the right-sided chambers or over the left ventricle. In the subgroup with cardiac enlargement, however, the group mean right atrial pressure significantly exceeded the mean pericardial pressure. Much of this difference was accounted for by two patients with pulmonary hypertension who presumably had right ventricular hypertrophy. It is reasonable to expect that as the thickness of the right ventricle increases, so does transmural pressure. That the pericardial pressure was being accurately reflected by the balloon transducer was suggested by the observation that following pericardiotomy, right atrial pressures either decreased or were unchanged despite an increase in stroke volume; this result would only be expected if left ventricular transmural pressures had increased after pericardiotomy.

On the basis of these data, it seems clear that pericardial constraint in humans is much greater than previously thought and that it represents a significant fraction of left ventricular intracavitary diastolic pressure even at normal volumes, at least in anesthetized supine patients. Moreover, a clinically useful estimate of the pericardial surface pressure can be obtained from a right atrial or right ventricular diastolic pressure measurement, at least in the absence of right ventricular hypertrophy. These data suggest that a clinically useful estimate of the left ventricular diastolic transmural pressure might be available from commonly used hemodynamic monitoring data by subtracting right atrial from pulmonary capillary wedge pressures.

The Pericardium and Load-Mediated Shifts in the Left Ventricular Pressure-Volume Relation

Let us return to our earlier postulate that the nitroglycerin-induced downward shift in the left ventricular diastolic pressure-volume relation might be explained by an unappreciated decrease in pericardial pressure. To test this hypothesis, we studied patients undergoing routine diagnostic cardiac catheterizations.[15] Pressures were measured in the left and right ventricles by micromanometer-tipped catheters, with the left ventricular volume estimated by two-dimensional echocardiography studies. Recordings were obtained before and approximately five minutes after the sublingual administration of nitroglycerin. Figure 5 shows the results from one patient.

We concluded from this study that the nitroglycerin-induced downward shift in the left ventricular diastolic pressure-volume relation was due to an undetected decrease in pericardial pressure. Moreover, the fact that the transmural diastolic pressure-volume relation was unaffected by nitroglycerin provides further evidence that the elastic properties of the myocardium were unaltered. Finally, we concluded that pericardial pressure was substantial, even in this group of patients in whom left ventricular intracavitary pressures were not particularly elevated nor the left ventricle dilated. We postulated that the nitrate produced this effect by causing venous dilatation with a resultant decrease in venous pressure and a decrease in right heart volume, which led to the decrease in pericardial pressure.[16]

Pericardial Pressure in Left Ventricular Failure

Let us now return to the data in Table 1 and explore the possible effect of the pericardium on the observed hemodynamics. The left ventricular transmural diastolic pressure before administration of nitroglycerin was 9 mm of mercury

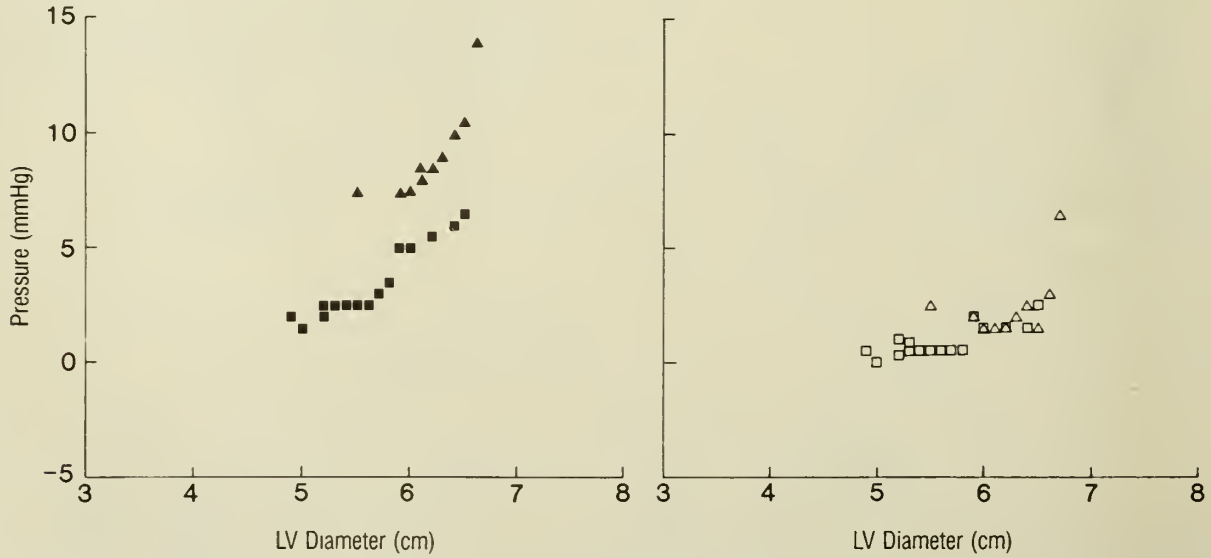

Figure 5.—Left Panel: Left ventricular (LV) intracavitary diastolic pressure-diameter relation before (▲) and after (■) sublingual administration of nitroglycerin in a patient undergoing routine cardiac catheterization. Note the parallel downward shift in the pressure-diameter relation after nitroglycerin was given. **Right Panel:** The same two cardiac complexes are depicted but transmural pressure—left ventricular minus instantaneous right ventricular pressure—has been plotted. The transmural pressure-diameter curve before (△) and after (□) administering nitroglycerin defines a single curve (from Smith et al,[16] with permission).

(pulmonary capillary wedge minus right atrial pressure). Following the initiation of the nitrate infusion, the estimated transmural pressure was still 8 mm of mercury, despite the rather significant decrease in left ventricular filling pressure. Since transmural diastolic pressure (preload) was maintained, we should not be surprised that the left ventricular stroke volume and cardiac output were also maintained. Obviously, a nitrate-induced decrease in afterload might have also contributed to the maintenance of stroke volume observed in this patient.

These data suggest that the acute elevation in left ventricular intracavitary diastolic pressure so characteristic of acute myocardial infarction is at least partially due to an unappreciated increase in pericardial pressure. In turn, nitroglycerin is very efficacious in the treatment of such patients because of its ability, through an action on the venous system, to decrease the pericardial pressure and thereby lower left ventricular intracavitary and pulmonary venous pressures. It seems likely that other vasoactive substances that shift the diastolic pressure-volume relation of the left ventricle act via a similar mechanism. Thus, sodium nitroprusside has an action similar to nitroglycerin, whereas angiotensin, which shifts the diastolic pressure-volume curve upward, probably increases the cardiac volume through its action on left ventricular afterload as well as on venous tone.[17]

Although it seems likely that substantial increases in left ventricular intracavitary diastolic pressure can be explained by the constraining effect of the pericardium on diastolic filling, one might not so readily accept that a similar mechanism would be operative in chronic heart failure. It is well recognized that the pericardium and heart both are capable of dilatation in patients with chronic heart failure; however, a recent study by Carroll and co-workers[18] suggests that the pericardium may affect diastolic filling in some of these patients. These workers studied 12 patients with dilated cardiomyopathy, all of whom had abnormal left ventricular diastolic properties. Administering nitroprusside produced a significant decrease in the left ventricular end-diastolic pressure; in five patients this was associated with a decrease in the left ventricular end-diastolic volume (diameter). In the remaining seven patients, however, sodium nitroprusside caused a parallel downward shift of the pressure-diameter relationship. Of importance is that this downward shift occurred in those patients with elevated right atrial pressures, and the magnitude of the downward shift corresponded to the magnitude of the decrease in right atrial pressure. Thus, it seems likely that even in patients with chronic biventricular heart failure and pronounced cardiomegaly, pericardial pressure accounts for a significant proportion of the elevated left ventricular intracavitary pressure.

Summary and Conclusions

Contrary to the conventional view, recent studies have documented that pericardial pressure both in animals and in humans is substantial and nearly equal to right atrial and right ventricular diastolic pressures. This observation provides a clinically reliable means to calculate effective left ventricular preload—pulmonary capillary wedge minus right atrial pressures. With this approach, our data suggest that the parallel downward shift in the left ventricular pressure-volume relation caused by nitroglycerin is due to an unappreciated decrease in pericardial pressure. It seems likely, therefore, that in most instances the substantially elevated left ventricular pressure noted in patients with acute left ventricular failure is due to an unappreciated increase in the pericardial pressure. Finally, recent data suggest that even in patients with chronic heart failure with notable cardiac enlargement, the pericardium can affect left ventricular diastolic filling. Our improved understanding of the hemodynamic importance of the pericardium promises to provide new insight into the pathogenesis of acute and chronic heart failure and may lead to new therapeutic options.

Questions and Answers

PHYSICIAN IN THE AUDIENCE: *If nitroglycerin works by this mechanism, it obviously involves some reduction in cardiac size. If we say that right ventricular size is reduced, how is performance of the right ventricle maintained?*

DR SMITH: This is a very difficult question, and we do not yet have a completely satisfying answer. Most important is the fact that the pericardium has a very steep pressure-volume relationship, so that a minor change in volume can result in a major alteration in pressure. Moreover, the atria probably also become smaller, perhaps even more so than the right ventricle. Also, we have shown that the pleural surface pressure in the cardiac fossa is elevated during congestion, and alleviation of this congestion by nitroglycerin might reduce the pleural component of the pericardial pressure, thereby increasing the transmural pressure in both ventricles at any given cardiac volume. Finally, we know that the nitroglycerin-induced afterload reduction helps to maintain left ventricular performance. How important this is to the right ventricle is unclear. Certainly, this question deserves further study with careful measurement of chamber dimensions and transmural pressures.

KANU CHATTERJEE, MD*: *You have attributed all of the effects from acute left ventricular failure and from nitroglycerin to an alteration in pericardial pressures. Do you think that ventricular interaction via the septum might also be involved?*

DR SMITH: There is no question that any intervention that alters the pressure-volume relation of one ventricle will also alter the pressure-volume relation of the other because of a shift in the position of the ventricular septum. Any degree of ventricular interaction via the septum is magnified by the presence of the pericardium. It is difficult to be certain of the relative contributions of the two mechanisms in any given situation. I accept your point that it is possible that the septum is involved to a greater extent than we are aware of in these particular studies.

DR ROOT: *We are told that the traditional management of right ventricular infarction is to give adequate fluid to maintain a cardiac output. I can see by invoking your mechanism that if we are too enthusiastic in our fluid administration, we could actually have a negative effect on cardiac output. Is this an accurate interpretation?*

DR SMITH: That is a very perceptive remark. The whole question of fluid administration in right ventricular infarction is one that I think merits reexamination. Such an approach clearly results in improved cardiac output in experimental animals in which the right-sided filling pressures are not

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particularly elevated over the preinfarction values and in humans when intravascular volume has been depleted by the inappropriate use of diuretics. The literature is not so clear concerning the efficacy of administering fluids to those patients with high right-sided filling pressures and low cardiac output. One can easily envision how such therapy in these patients might cause a decrease in left ventricular transmural pressure by increasing pericardial pressure and could further compromise cardiac output.

DR BOUSHEY: *Is there any evidence that the pericardium can vary its volume?*

DR SMITH: Not that I am aware of. The histologic appearance of the pericardium does not suggest that active changes would be likely—that is, there are no muscle cells. Of course, the pericardium does undergo stress relaxation, although this occurs only slowly and with changes that are so small that they do not seem to be important with respect to the phenomena we have been discussing.

PHYSICIAN IN THE AUDIENCE: *Could alterations in pericardial pressure be accounted for by vascular turgor?*

DR SMITH: We do know that the vascular supply to the pericardium is sufficient to allow rapid absorption of fluid from the pericardial space. I personally doubt that there is enough turgor induced by the vascularity of the pericardium to explain a 20 mm-of-mercury downward shift in the diastolic pressure-volume relation. Admittedly, this possibility has not been adequately examined.

PHYSICIAN IN THE AUDIENCE: *In those situations in which cardiac performance is compromised by chronic left ventricular failure, would it be a reasonable hypothesis to suspect that pericardiectomy might be beneficial?*

DR SMITH: It is an interesting hypothesis. It is widely believed that greyhounds can run faster if the pericardium has been removed, presumably because they develop a larger stroke volume, and it has been shown recently that a pericardiectomized dog has greater exercise capacity and myocardial oxygen consumption. I am aware of only one report of pericardiectomy being used in humans to manage dilated cardiomyopathy. It was an uncontrolled observation, although the author suggested that improvement occurred.

PHYSICIAN IN THE AUDIENCE: *Why don't patients who have pericardiectomy have pronounced cardiac enlargement?*

DR SMITH: This probably reflects a number of factors. There is probably some scarring, which tends to replace pericardial function. In addition, the lungs, esophagus, and other chest structures also contribute to extracardiac constraint. In a recent study in dogs, we showed that the addition of positive end-expiratory pressure to ventilated animals caused an increase in the pericardial pressure. Conversely, expanding the cardiac volume by administering intravenous fluid caused an increase in the pleural pressure measured adjacent to the heart. Overall, approximately a third of external constraint to the left ventricle was contributed by the lungs. Thus, cardiac dilation is likely limited by the constraint provided by extrapericardial structures.

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Epitomes

Important Advances in Clinical Medicine

Nuclear Medicine

The Scientific Board of the California Medical Association presents the following inventory of items of progress in nuclear medicine. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, research workers, or scholars to stay abreast of these items of progress in nuclear medicine that have recently achieved a substantial degree of authoritative acceptance, whether in their own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Nuclear Medicine of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to Division of Scientific and Educational Activities,
California Medical Association, PO Box 7690, San Francisco, CA 94120-7690

Metaiodobenzylguanidine in the Diagnosis of Pheochromocytoma and Neuroblastoma

METAIODOBENZYLGUANIDINE (MIBG), a guanethidine derivative resembling norepinephrine in structure, was originally described by investigators at the University of Michigan; it can be labeled with iodine 123 or iodine 131. After administration, MIBG is bound to norepinephrine binding sites and subsequently stored in the neurosecretory granules of neuroectodermal cells located in the adrenal medulla, pheochromocytoma, neuroblastoma, and some other tumors of neural crest origin.

Only 25% of pheochromocytomas are diagnosed before death. The morbidity and mortality in patients with these lesions is high because of stroke, myocardial infarction, and the complications of hypertension. In unrecognized pheochromocytoma, catecholamine crisis and death can occur during the induction of anesthesia for an unrelated problem. Since 10% to 20% of pheochromocytomas are extra-adrenal or multifocal, MIBG imaging is establishing its place in the characterization of adrenal or periadrenal masses incidentally encountered in computed tomographic scans.

Imaging is usually done 24 hours after giving the patient MIBG. Images can be obtained up to 48 hours after administration with iodine 123 and even later with iodine 131. Lesion image contrast tends to improve with time, and faint normal adrenal medullary localization rarely is a problem because tumors typically show abundant uptake. Hepatic, bladder, and occasionally colonic localization normally is seen early—3 to 24 hours. Myocardial localization appears to be quantitatively related to catecholamine binding site concentration.

Reported sensitivities of MIBG imaging for the diagnosis of pheochromocytoma range between 70% and 90%. Specificities of 100% have been encountered in large series reported at both the University of Michigan and the University of California, San Francisco. Metaiodobenzylguanidine also has been useful in staging neuroblastomas and in preoperative categorizing of abdominal masses in children.

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Gallium Studies in Patients With the Acquired Immunodeficiency Syndrome (AIDS) and the AIDS-Related Complex

GALLIUM GA 67 CITRATE IMAGING has been a useful tool in evaluating patients with the acquired immunodeficiency syndrome (AIDS) or the AIDS-related complex (ARC). In identifying *Pneumocystis carinii* pneumonia, the noninvasive gallium scan, because its sensitivity is greater than 90%, is an excellent screening tool for the early detection of asymptomatic opportunistic infection with or without radiographic abnormality and as a triage device to direct the appropriate patients to bronchoscopy and bronchoalveolar lavage when tissue-specific diagnosis is needed. For example, in a group of about 30 patients studied by Kramer and colleagues, the relative sensitivity of a chest x-ray film, when compared with the gallium scan, was only 50%. Gallium scans are thus useful in identifying clinically occult *P carinii* pneumonia or may lead to a reclassification from ARC to AIDS in those patients who are asymptomatic and have a normal chest x-ray film. The pattern of gallium localization in the lungs in these patients is mainly diffuse, with intense increased uptake in both lungs, although focal localization has been noted in some patients. The focal pulmonary pattern has also been seen in patients with *Mycobacterium avium-intracellulare* and bacterial pneumonia. Other than *P carinii* pneumonia, the diffuse pattern is also seen in pulmonary infections caused by cytomegalovirus, *Cryptococcus, Toxoplasma,* and in interstitial fibrosis. Sputum retrieval, bronchial washings, or open lung biopsy must be done for a definitive diagnosis.

M avium-intracellulare is a common infection in AIDS patients. Intrathoracic regional lymph node localization of gallium 67 should suggest *M avium-intracellulare* lymphadenitis; the finding has a 90% positive predictive value. Lymphoma may present with a similar pattern, however, making tissue diagnosis imperative.

The intestine is one of the most common organs for opportunistic infections in patients with AIDS. Intense gallium

colonic uptake, especially with good bowel preparation, may suggest infection of the intestinal tract or inflammation of the intestinal mucosa. Further investigations, such as stool examination, microbiologic studies, and, if appropriate, colonoscopy with biopsy, should be done.

About 95% of the neoplasms occurring in AIDS patients are either Kaposi's sarcoma or non-Hodgkin's malignant lymphoma. Kaposi's sarcoma is common in AIDS patients and accounts for approximately 85% of cancer in male homosexuals. To date, no evidence of gallium uptake in the lesions of Kaposi's sarcoma has been reported. The gallium scan is helpful in differentiating pulmonary Kaposi's sarcoma from infection in AIDS patients with this cancer. In such patients, a normal gallium scan with an abnormal chest x-ray film increases the likelihood of pulmonary Kaposi's sarcoma.

About 4% to 10% of AIDS patients have non-Hodgkin's lymphoma. High-grade lymphomas usually have intense gallium uptake, while lower grade lymphomas usually have mild gallium uptake. The degree of uptake in the initial gallium scan appears to be inversely related to the survival times of these patients. Patients with non-Hodgkin's lymphoma frequently have extranodal involvement; gallium scanning may be superior to computed tomography scanning for staging purposes.

In conclusion, gallium scanning is clinically very useful in patients with AIDS. Because its sensitivity is greater than 90%, it can differentiate ARC from asymptomatic AIDS in the early stage of *P carinii* pneumonia. When used in patients with minimal pulmonary symptoms, gallium scans can noninvasively identify those who have infection and would benefit from bronchoscopy or lung biopsy.

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Radionuclide Evaluation of Renal Transplants

RENAL SCINTIGRAPHY has proved useful in assessing the complications of renal transplantation. Flow, morphology, and function can be evaluated without substantial risk. Complications can be divided into two categories: renal parenchymal pathology, including acute tubular necrosis (ATN) rejection, and cyclosporine nephrotoxicity; and anatomic lesions, including vascular obstruction, perinephric fluid collections, urine leak, and obstruction. The clinical findings in many of these processes are nonspecific and, in the case of rejection, may be obscured by routine immunosuppressive therapy.

The two most important radioactive nuclides in transplant imaging are technetium Tc 99m pentetic acid (DTPA) and iodohippurate sodium I 131 (Hippuran I 131). Although many abnormalities can be detected with either agent, they are in some respects complementary, and often both are used. ^{99m}Tc DTPA has better imaging properties and gives much better statistics in the usual doses, whereas iodohippurate ^{131}I is principally secreted by the tubules and is helpful when certain parenchymal lesions may be present ("polyuric" ATN or cyclosporine toxicity) with relatively normal renal flow. Both studies can be readily quantified in a variety of ways using time-activity curves and, on occasion, by sampling the plasma and urine activity. A baseline renal scan is usually done within 24 hours of transplant placement, with follow-up studies as clinically dictated.

Among the parenchymal lesions, acute tubular necrosis is characterized by relatively normal flow on the DTPA study, with very poor excretion of iodohippurate ^{131}I and poor accumulation of DTPA in the urine. As ATN resolves, the iodohippurate ^{131}I program assumes a more normal configuration. In transplant rejection, the renal perfusion is substantially diminished and renal tubular function is abnormal. A prominent collecting system ("pseudo-obstruction") may be seen in cases of rejection as well. Cyclosporine toxicity has a similar scintigraphic appearance to ATN, with diminished tubular function out of proportion to the change in renal perfusion. Many other agents have been proposed to detect rejection, including technetium Tc 99m sulfur colloid, gallium Ga 67 citrate, fibrinogen I 131, and leukocytes and platelets labeled with indium In 111. Most of these agents have proved too nonspecific to be useful, but the use of platelets labeled with ^{111}In appears promising.

Anatomic lesions are as a group best shown with ^{99m}Tc DTPA flow studies and sequential static images. Renal vascular occlusion is seen as a complete absence of renal perfusion to the kidney or the segment of kidney involved. Renal artery stenosis does not have a specific scintigraphic appearance, but the scan does show decreased perfusion in the absence of rejection by other criteria. Hematomas and lymphoceles are seen in scintigraphic studies as photopenic defects or possibly a "halo" near the transplant. Urinomas appear initially photopenic but gradually fill in with activity as tracer is excreted into the collecting system. To show the filling of a urinoma, it may be necessary to obtain postvoiding images. Occasionally obstruction of a transplanted kidney is seen that is scintigraphically similar to an obstructed collecting system in a nontransplanted kidney.

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Detection of Gastrointestinal Bleeding

ACUTE UPPER GASTROINTESTINAL BLEEDING is most often caused by gastric or duodenal ulceration, gastritis, and varices. Conservative treatment—lavage, bed rest, volume replacement, and sedation—will benefit 80% of patients with such bleeding. Lower gastrointestinal bleeding is commonly due to diverticular disease, angiodysplasia, inflammatory bowel disease, and neoplasia. Bleeding is usually intermittent.

Care and management of these patients has remained a problem, but there is now increasing interest in the scintigraphic detection of gastrointestinal bleeding. The use of technetium Tc 99m sulfur colloid for the scintigraphic detection of gastrointestinal bleeding has largely been superceded by blood pool imaging.

Winzelberg and colleagues proposed using ^{99m}Tc-tagged red blood cells as a blood pool tracer for detecting gastrointestinal bleeding. Any site actively bleeding within a 24 to 36 hour interval is potentially detectable. Most published series give a sensitivity and specificity for this procedure of about 90%. Bleeding rates of 0.2 to 0.4 ml per minute can be detected. Sequential one-minute views of the abdomen following tracer injection can be stored on computer and displayed in cine mode. This technique allows computerized subtraction of activity in known large blood vessels and other vascular structures. By following the cine display, one may detect the position of extravasated blood at an active bleeding site. A negative study result may obviate the need for emergency angiography and using contrast in patients who are unstable and often elderly.

^{99m}Tc as pertechnetate—not complexed to erythrocytes—can be used to locate ectopic gastric mucosa: Meckel's diverticulum and Barrett's esophagus. Meckel's diverticulum is the most common cause of gastrointestinal bleeding in children younger than 3 years. In a large series of predominantly pediatric patients, Sfakianakis and Conway found that the scanning procedure had a sensitivity of 85%, a specificity of 95%, and an accuracy of 90% for surgically proved ectopic gastric mucosa.

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Emergency Nuclear Medicine Studies

In recent years nuclear medicine studies have played an ever-increasing role in the emergency setting. Several developments have contributed to this change: nuclear medicine services are more widely available, new radiotracers have become available, image quality has improved, and radiopharmaceuticals are easier to prepare.

Lung scans have been a standard test for detecting acute pulmonary emboli for many years. More recently, radionuclide biliary studies are commonly used in detecting cystic duct obstruction in acute cholecystitis, common duct obstruction, or bile leak. Tagged red blood cell studies are used to detect and localize acute gastrointestinal bleeding and radionuclide venograms to identify acute thrombophlebitis and superior vena cava obstruction.

In addition, a liver-spleen scan is useful in diagnosing fracture, laceration, and hematoma; renal studies in renal artery obstruction and acute renal failure; testicular studies in torsion and acute epididymitis; pyrophosphate cardiac studies in acute myocardial infarction and cardiac contusion; and brain scans in acute viral encephalitis and for determining brain death. The early determination of brain death has taken on increasing importance because of organ transplant programs.

Emergency bone scans may show fractures missed on radiographs because separation has not yet occurred. They can provide an overview of the entire skeleton in a possibly battered child. Bone scans are also helpful in detecting stress fracture, early acute osteomyelitis, septic arthritis, and avascular necrosis.

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A Simple Bedside Method for the Prompt Diagnosis of Brain Death

Because brain function is the essence of human life, death of this organ is recognized as a criterion of death. Indeed, attempts at resuscitation following cardiac arrest are aimed at sustaining the brain. The Harvard criteria, established in 1968, require 24 hours of electrocerebral silence in appropriate comatose patients in the absence of drug intoxication or hypothermia. A totally flat electroencephalogram is often difficult to obtain reliably. Screening for a variety of drugs required by these criteria is time-consuming and may delay diagnosis. While undue delay is most critical in the case of potential organ donors, a futile attempt at maintaining life in a brain-dead person is very costly and often causes unnecessary anguish for relatives.

Demonstration of a deficit in blood flow to the brain is diagnostic of brain death and is not related to the cause of coma. This absence of circulation can be shown angiographically. There is, however, a justifiable reluctance to moving these fragile, comatose patients, who may or may not be brain dead, from their bedside life support systems to submit them to angiography when they will not benefit directly from this procedure. A critical deficit in cerebral blood flow can be reliably shown by nuclear imaging procedures. Using a portable γ camera, the study can be done at a patient's bedside. The cerebral transit of an intravenously injected bolus of an agent such as technetium Tc 99m pertechnetate, pentetic acid (DTPA), or glucoheptonate can be followed by rapid sequential imaging of the head. This dynamic sequence will reliably show the absence of intracerebral blood flow. A static anterior image of the head following the flow study will, in the majority of patients, be confirmatory by showing an absence of activity in the sagittal sinus. In a small number of patients, the sagittal sinus may be visualized even in the absence of brain activity. This is presumably due to ingress of the imaging agent through the emissary veins. This in no way negates an abnormal flow study result.

This nuclear medicine study is essentially free of risk, simple, and absolutely reliable—except in infants. The study may be repeated for further confirmation or if the first examination was technically unsatisfactory. The more up-to-date and rapid diagnostic criteria for the diagnosis of brain death

are included in the recommendation of the consultants on the President's Commission on the Diagnosis of Death. The nuclear medicine test is recommended as confirmatory by these consultants.

It is worth noting that this test does not evaluate the posterior fossa. Other tests are available for this and, in any case, in the presence of total supratentorial brain death, demise of the posterior fossa will occur within a relatively few hours.

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Simple Evaluation of Thyroid Function

PHYSIOLOGIC AND CLINICAL STUDIES have shown clearly that primary thyroid failure is associated with a compensatory rise in pituitary thyroid-stimulating hormone (TSH) secretion, while an excess of circulating thyroid hormones is associated with a negative feedback inhibition of TSH secretion. Until very recently commercial assays for TSH could detect abnormally high serum levels but were not sensitive enough to distinguish abnormally low values from those found in most normal persons. Consequently, the TSH assay was used primarily to confirm or establish the diagnosis of hypothyroidism. Less commonly, the failure of the serum TSH to rise in response to the administration of thyrotropin-releasing hormone was used to confirm the diagnosis of hyperthyroidism in clinically equivocal cases.

The advent of the ultrasensitive test for thyroid-stimulating hormone, which is capable of detecting levels in serum below those found in normal subjects, is revolutionizing the laboratory assessment of thyroid function. All forms of hyperthyroidism, with the exception of the rare TSH-secreting pituitary adenoma—Graves' disease, toxic thyroid adenoma, Hashimoto's thyroiditis, subacute thyroiditis, or excessive ingestion of thyroxine or triiodothyronine—are associated with serum TSH values well below the defined and measurable normal range of about 0.4 to 6.2 μU per ml. The new type of TSH assay uses two monoclonal anti-TSH antibodies recognizing different determinants of the thyroid-stimulating hormone molecule. Typically, the serum TSH level in thyrotoxic persons is suppressed to 0.05 μU per ml even if clinical signs of disease are mild. The physiologically hyperthyroid state can be diagnosed with assurance even when a patient is asymptomatic; not infrequently, this occurs in a hyperthyroid person taking antithyroid drugs, in hypothyroid patients taking levothyroxine sodium, or in a patient with a thyroid nodule or with surgically treated thyroid carcinoma who is on thyroxine-replacement therapy at a dose designed deliberately to suppress maximally the serum TSH level. Persistently suppressed levels of TSH during treatment with antithyroid drugs indicate that the treatment is inadequate. A fully suppressed serum TSH level correlates well with the failure of serum TSH to rise after administration of thyrotropin-releasing hormone, so the latter test should rarely be needed to confirm thyrotoxicosis or to establish that suppressive thyroxine treatment is adequate in patients with treated thyroid carcinoma.

A parallel measurement of the serum free thyroxine level is usually recommended to assess the biochemical magnitude of hyperthyroidism. Obvious clinical toxicity is usually associated with values well above the normal range; however, mild hyperthyroidism, as defined by serum TSH suppression, is not infrequently associated with free thyroxine levels in the upper portion (1.6 to 2.3 ng per dl) of the normal range (0.8 to 2.3 ng per dl). Critically ill patients with nonthyroidal illness who are not receiving dopamine have normal pituitary-thyroid function.

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Dipyridamole Myocardial Perfusion Scintigraphy

MYOCARDIAL PERFUSION SCINTIGRAPHY using thallium 201 during dynamic exercise is now well established as an important clinical aid for the diagnosis and prognosis of coronary artery disease. A large fraction of patients, a third or more, with known or suspected coronary disease are ill, debilitated, or timid, however, and cannot undergo dynamic exercise stress testing. Others, such as patients after myocardial infarction, should not be or generally are not submitted to a maximal exercise effort. Nevertheless, symptoms in these patients are often atypical or absent despite the fact that they may harbor the most severe, life-threatening disease. Compounding the problem is the fact that many of them often face a significant surgical intervention. Patients with peripheral vascular disease claudicate, and their limited activities prevent the early appearance of cardiac symptoms. Yet, their major morbidity and mortality relate to associated, frequently occult, coronary disease, which is the leading cause of postoperative complications.

Dipyridamole inhibits circulating adenosine deaminase, resulting in reduced degradation and increased levels of the potent arteriolar dilator, adenosine. Administered intravenously, the agent has significant effects on the coronary resistance vessels, the small arterioles, resulting in a threefold to fivefold increment in coronary artery flow through normal vessels. This flow augmentation is limited by a fixed stenosis, however. Animal experiments indicate differential augmentation of coronary perfusion in both normal and stenotic vessels. Coronary flow demands, however, are generally not increased and ischemia is rarely documented, possibly due to a "steal" effect or to an actual flow reduction.

A saline solution containing 0.56 mg per kg of dipyridamole is infused over four minutes with full symptomatic and hemodynamic monitoring. Ingestion of a dipyridamole slurry has also been reported to be effective. Thallium is administered at seven minutes, and images are acquired shortly thereafter and four hours later at redistribution, when basal flow distribution of the radionuclide is restored. Uniform flow augmentation in the absence of significant coronary lesions produces a homogeneous radionuclide distribution and a normal image. The presence of pathophysiologically signifi-

cant coronary artery lesions causes heterogeneous flow augmentation and perfusion image defects. These defects generally disappear on redistribution imaging if they are not related to regions of scarring.

Effects of the drug are generally benign, bringing a mild fall in systolic blood pressure and a mild increment in heart rate. Side effects are also usually mild and relate to systemic vascular dilation with headache, flushing, and nausea. Although ischemic indicators are uncommon, an occasional dramatic ischemic response may be seen and fatalities have been reported. Drug effects can be quickly reversed by intravenous administration of aminophylline, which specifically blocks the vascular adenosine receptors. While the functional correlate of such induced ischemia may be qualitatively assessed in some cases with echocardiography, that method will fail to identify the much more frequently induced perfusion heterogeneity not associated with ischemia.

The diagnostic sensitivity of the imaging method approaches that related to dynamic exercise imaging—in the range of 80% to 90%. Specificity is also high. The test has proved extremely useful and has been noted to influence diagnosis and management in almost 80% of the patients evaluated. Additionally, the method, like dynamic exercise perfusion evaluation, appears to have prognostic value. In several studies done in patients before peripheral vascular and other noncardiac operations, perioperative coronary events were seen only in those with reversible scintigraphic defects. Further, patients with reversible defects were those having coronary events after subendocardial infarction. Test safety in patients after acute infarction and in those with unstable angina has not been fully established.

This pharmacologic method, not yet approved by the Food and Drug Administration, soon is likely to be made widely available for the evaluation of known or suspected coronary artery disease in patients who cannot or should not undergo dynamic exercise evaluation. Despite the apparent advantages, the value of stress-related data and the superiority of exercise-related images make dipyridamole perfusion imaging no substitute for conventional exercise evaluation.

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Editorials

The Medical Risks of Cocaine

ELSEWHERE IN THIS ISSUE is a rather thorough review of the potential medical hazards of the illicit use of cocaine, and a perusal of the bibliography of this review aptly reflects the fact that most of our current knowledge regarding cocaine abuse has arisen in the past decade. Indeed, as cocaine was rediscovered as a recreational drug in the 1970s, so, too, are the medical consequences of its widespread and uncontrolled use being rediscovered.

Cocaine is a unique local anesthetic in that it produces local vasoconstriction and also stimulates both the cardiovascular and the central nervous systems. Its discovery as a local anesthetic during the Civil War era was of major historic importance. It immediately became popular for nasopharyngeal and oropharyngeal operations and was even marketed as a remedy for toothaches. Its use for ophthalmic surgery was abandoned because of its propensity to produce corneal ulcerations. Before long, the stimulant and psychotropic properties of cocaine were realized, and this further increased its popularity among the lay public and the medical profession, as well.

Various concoctions with cocaine were marketed as tonics that would allegedly cure or ameliorate a variety of ailments—everything from impetigo to impotence. Sigmund Freud loudly proclaimed that cocaine had important psychotherapeutic properties and, furthermore, could be used as a cure for opiate addiction. By the turn of the century, cocaine was widely regarded as a wonder drug: a local anesthetic, a psychotherapeutic agent, and a cure-all that made you feel good, too. The few who warned of the dangers of cocaine were largely ignored.

As the unchecked and widespread use of cocaine continued, reports of adverse reactions began to surface. Anecdotes of cocaine-induced criminal behavior, convulsions, hyperthermia, psychotic reactions, and sudden death began to change the popular perception of cocaine as a wonder drug. Medical observations, animal experiments, and common experience all revealed the highly addictive nature of cocaine, as well. Finally, the drug was banned from popular consumption by the Harrison Narcotics Act of 1914.

Cocaine remained fairly popular as a topical anesthetic for surgery of the nose and throat because of its vasoconstrictive properties. As a recreational drug, however, cocaine was virtually forgotten for over half a century. Then the social turbulence of the 1960s engendered a renewed interest in the drug. By the mid-1970s cocaine was regarded as a safe, nonaddictive stimulant that was ideal as a recreational drug. The only hint that cocaine might be dangerous came from anecdotes a half century old, and these lacked scientific validity. Certainly, there was very little in the medical literature of the 1970s to suggest any serious consequences from cocaine use. Subsequent reviews both implicitly and explicitly indicated that untoward reactions to cocaine were unusual and unlikely.[1,2]

Although the possibility of dependency and tolerance to cocaine was unclear, there was general agreement that the drug was not "physically addictive," although, like most anything, there was the implication that it could be "psychologically addictive" for the mentally weak. Unlike the opiates and depressant drugs that rendered users into a state of lethargic intoxication, the perception was that cocaine stimulated one to the epitome of professional, intellectual, and social performance. Its illegal status appeared to be based on ill-founded anecdotes and moral perceptions no longer applicable to the enlightened times of the latter 20th century. And the legal classification of cocaine as a narcotic tended to support the apparent absurdity of maintaining it in a restricted status.

The expense and mystique of cocaine, its stimulant properties, and the belief in its safety all combined to make the recreational use of this drug popular among the affluent and the professionally successful—the role models of society. To snort cocaine was chic and trendy. Illicit production rapidly increased to meet the growing demand, and the widespread, unchecked use of the drug soon permeated all socioeconomic strata throughout the United States. Consequently, we are now repeating the lessons of history. Cocaine was known to be a dangerous drug in the first decade of this century; today, we are merely providing the scientific and medical validity of those earlier conclusions, as summarized by Bates in this issue of the journal.

The potentially lethal consequences and medical hazards of most so-called recreational drugs arise because of three factors: overdose, leading to central nervous system depression; intoxication, leading to an inability to effectively function in a given environment—driving an automobile, for example; and physiologic or structural damage from long-term consumption. Ten years ago, the toxic reactions to cocaine were generally regarded as a self-limited overstimulation of the central nervous system and sometimes the cardiovascular system. On rare occasions, cocaine toxicity could produce grand mal seizures followed by respiratory collapse and death. At that time, the only peculiar trait about cocaine toxicity was that the untoward reactions, particularly convulsions, were not always accompanied by prodromal signs or symptoms, and the reactions did not always appear to be dose-related. There was no evidence that cocaine intoxication was related to traumatic death or violent behavior, and there did not appear to be any adverse effects from long-term consumption, except, of course, for a possible perforation of the nasal septum. Intravenous users of cocaine were simply thought to be subject to the same medical complications of any intravenous drug abuser.

We are now aware that cocaine, in fact, is highly addictive, has numerous medical hazards, and may kill by a variety of mechanisms.[3] Acute cardiovascular events, manifested as catechol excess, include vascular rupture from surges in blood pressure and potentially lethal myocardial rhythm disturbances, and there is growing evidence that cocaine may actually induce coronary vasospasm. Although the medical hazards of the long-term consumption of cocaine are generally unknown at this time, there is a growing suspicion that habitual use may result in myocarditis—and potentially, therefore, myocardial fibrosis—cardiomyopathy, and coronary artery stenosis. The obvious implication is that cocaine users who cease their consumption may have already caused irreversible structural damage that may progress to serious and potentially lethal medical problems.

Unfortunately, the incidence and extent of the medical complications of cocaine, including sudden death, are un-

known. In part, this is because drug testing is not routine and, in many situations, is not even feasible. Also, a history of recreational drug use may not be elicited because the question was not asked or because the response was not truthful. Nonetheless, considering the extent of cocaine use today, it is imperative that efforts be made to delineate the incidence and types of cocaine-induced medical problems.

Of equal importance is that physicians be aware that the underlying disease they are treating, or should be treating, is that of addiction; the drug-induced medical complications are merely a manifestation of that disease, or a mechanism of death. Because the disease of addiction has identifiable criteria—compulsion, loss of control, and continued use despite real or potential consequences—these should be recognized and treated (directly or by referral) along with the presenting illness or complaint. Over the past decade, our understanding of addiction and its medical complications has come into sharper focus. These concepts, however, are not uniformly or adequately taught in most medical schools and are not yet widely disseminated among the members of the medical profession in general. This is a serious deficiency considering the enormous economic, social, and medical consequences of substance abuse. Until medical education is adequate in this regard, the prevention of drug abuse and its appropriate treatment will continue to be deficient.[4] And as substance abuse remains virtually unchecked, we will continue to learn more about the acute and chronic effects of drugs like cocaine.

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The Higher Calling—Time to Be Born Again?

THESE ARE TIMES when more than a few physicians are having some gnawing qualms of conscience about their feelings or attitudes in patient care. Others, having tried to serve in the highest traditions of their calling, may not be having so much trouble with their consciences, but rather, look with concern or even dismay at what seem to them to be signs of deterioration in what they had thought to be the higher calling of their profession. And, alas, there are those among us who seem to have lost any sense of a higher calling, if indeed they ever thought there was one. Perhaps it was ever thus.

The times are indeed difficult. If there was or is a higher calling for physicians, then what was it or what is it, and if we are beginning to lose it, are we losing something important? Most physicians seem to sense that there is indeed a higher calling—a dedication of one's self and one's professional knowledge and skills as a physician to serving one's fellow human beings, that is, patients and the public. If this is what it is, albeit all too simply stated, it surely is undergoing mighty assaults by powerful forces in today's health care environment. An untraditional emphasis on dollars; myriads of rules, regulations, and laws that impinge upon the professional services physicians are trying to render; and the many administrative bureaucracies within which much of today's medical care is rendered are the avenues of assault.

Most physicians, when they originally decided upon a career in medicine, did so because of a fascination with modern biomedical science, a desire to work with people, and a wish to do something they consider good and useful with their lives. They have accepted serving other people by these means as their calling. But the powerful environmental forces alluded to above are now having so much influence on the daily practice of medicine that it seems appropriate to begin to ask ourselves whether something really important is beginning to be lost, both for many individual physicians and for the profession as a whole. Have we begun to lose sight of the higher calling that for many of us was one of the main reasons we decided on a career in medicine? Are too many of us beginning to be so diverted by the nightmares of dollars, regulations, laws, court actions, and the administrative bureaucracies of health care that we are actually losing many of the satisfactions for which we entered medicine in the first place? This may be happening more often than one would like to think.

I wonder if the time has not come for frustrated and sometimes angry physicians—and there are many—to remember the reasons why they chose to become physicians in the first place, and then to be born again, to use a contemporary term, in a personal renewal of their original commitment to medicine. The dollars, the regulations, the laws and the administrative bureaucracies of health care might then be seen in a new and more balanced perspective and more readily recognized for just what they are—the conditions under which society has determined medicine must now be practiced, onerous though this may be. A personal and collective reaffirmation of a higher calling for physicians and medicine, with a primary concern with service to patients and the public, will help us all, individually and collectively, to get on with what physicians and medical practice are really all about.

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extraction solvent ("Key Chemicals: Methylene Chloride," *Chemical Engineering News*, 1980, vol 58, p 11). Therefore, the potential exists for methylene chloride exposure from a wide range of environmental sources, from industrial activities, and from the use of consumer products. Methylene chloride readily enters the body through the lungs due to its high volatility. Methylene chloride can also be absorbed through the skin in significant amounts.[9] Methylene chloride is a known hepatotoxin in both humans[10-12] and animals.[13-15] Methylene chloride is metabolized producing carbon monoxide. The production of carbon monoxide is responsible for most of the acute effects of methylene chloride intoxication, and the severity of an acute exposure can be assessed by determining carboxyhemoglobin levels.

Both of the cases presented satisfy the criteria for occupationally induced illness.[16] Our first purpose in presenting them is as a reminder that occupational diseases do not usually present with unique findings that allow easy differentiation from nonoccupational causes. The possibility of an occupational disease can result in both an inaccurate diagnosis and inappropriate treatment. In addition, the patient may be denied the benefits of financial compensation for work-related illnesses.

Second, these cases involve chemically induced hepatitis, a phenomenon whose incidence rate is largely undefined. It may well be that many cases are mild and go unrecognized. Cases involving only mild elevation in liver enzyme levels may be attributed to other factors, including spurious laboratory results. When detected, abnormalities in liver studies should be observed for a return to normal. Laboratory studies providing a more sensitive assessment of liver function include the indocyanine green clearance test,[17] the antipyrine clearance test,[18] and fasting levels of serum bile acids.[19] Workers with confirmed solvent-induced chemical hepatitis may not be able to return to occupations that expose them to hepatotoxic chemicals, as persistent clinical sensitivity will result in the rapid development of hepatitis following reexposure.

The risk of long-term sequelae from transient liver injury is unknown. In the case of methylene chloride, recent data suggest a potential for carcinogenicity in animals.[20] Where a medical surveillance of workers is done, evaluation of hepatic status, including medical and occupational history, physical examination, and appropriate laboratory studies, should be part of the program for workers exposed to known hepatotoxins.

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Blastomycosis in Saskatchewan

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BLASTOMYCOSIS, caused by the dimorphic fungus *Blastomyces dermatitidis,* is endemic along the Mississippi, Missouri, and Ohio river basins in the United States and in Manitoba, Quebec, and an area north and east of Lake Superior in Ontario.[1-3] The natural habitat of this organism remains a mystery, although it has been isolated from soil on a few occasions.[4-6] Although one case originating in Alberta was reported in 1982, blastomycosis is not known to be endemic to western Canada.[7] We document here three cases in persons who to our knowledge had no significant residence outside Saskatchewan.

Reports of Cases

In reviewing microbiologic records at University Hospital in Saskatoon between 1972 and 1986, we found three cases in which *B dermatitidis* had been identified by either cultural or histologic means. All charts were reviewed, and, when necessary, additional information was obtained by contacting the families or attending physicians or both. Details of travel and places of residence were obtained in all cases.

Case 1

The patient, a 56-year-old power plant mechanic from Saskatoon, was admitted to hospital in March 1973 because of cough and fatigue for eight months. The cough was de-

(Vallabh V, Martin T, Conly JM: Blastomycosis in Saskatchewan. West J Med 1988 Apr; 148:460-462)

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scribed as initially nonproductive but later as minimally productive. For the four weeks preceding admission he had hemoptysis, a dull aching left-sided chest pain, nausea, poor appetite, and a weight loss of 3.1 kg (7 lb). His past history was unremarkable except for 40 pack-years of smoking. Detailed travel and residence histories revealed only that he had taken brief holidays to North Dakota two years previously and Wyoming eight months previously.

On physical examination, he was thin and asthenic appearing; the only abnormality found was a perforated right tympanic membrane. Laboratory investigations elicited a hemoglobin of 13.5 grams per dl and a leukocyte count of 14.9 $\times 10^3$ per μl. The chest radiograph showed a mass lesion in the posterior segment of the left upper lobe. Tomograms confirmed the presence of a mass lesion along with complete collapse of the left upper lobe.

Bronchoscopy with biopsy and brushings were nondiagnostic, and a thoracotomy and open-lung biopsy were done. The pleura in the region of the left upper lobe was studded with collagenous-appearing plaques. On histologic examination there was granulomatous inflammation of the lung and the presence of yeast, suggesting either *Cryptococcus* or *Blastomyces.* Subsequent cultures confirmed the yeast to be *B dermatitidis.* The patient was successfully treated with a total course of 1.5 grams of amphotericin B.

Case 2

The second patient was a 58-year-old woman, a homemaker from Mistatim, Saskatchewan, who had a longstanding history of diabetes mellitus and ischemic heart disease. In September 1980 she was admitted to hospital with a 12-week history of cough, anorexia, weakness, and many small ulcerative skin lesions, some of which were draining purulent debris. She also had pain in the left heel. Ten days before admission to University Hospital, she was admitted to the local hospital with a tentative diagnosis of "bacterial pneumonia," and ampicillin and gentamicin sulfate were administered intravenously. She continued to have cough productive of a thin, mucoid sputum and because of failure to respond was transferred to University Hospital. She had had a tonsillectomy in 1950, excision of a benign intracranial tumor in 1952, insulin-dependent diabetes mellitus since 1964, and degenerative joint disease of the left knee since 1977. A travel and social history revealed that she had been born and raised on a farm near Prudhomme, Saskatchewan, and had moved to Mistatim only five years previously.

On physical examination she was pale, thin, and appeared ill, with tachycardia, tachypnea, and a temperature of 38.9°C (102°F). Many small ulcers, some with purulent drainage, were present on the trunk and extremities. The left heel was tender, with edema of the dorsum and the lateral aspect of the foot. She had oral thrush. There were diffuse inspiratory and expiratory crackles throughout both lung fields. Laboratory studies showed a hemoglobin of 12 grams per dl, with a leukocyte count of 10.9 $\times 10^3$ per μl. Electrolytes and tests of renal function gave normal values. The chest radiograph showed a diffuse reticulonodular interstitial pattern. Initial blood cultures were negative, and sputum Gram's stain and culture revealed abundant pus cells, no bacteria, and a light growth of *Staphylococcus.*

Therapy with gentamicin, cephalothin sodium, isoniazid, and rifampin was instituted with a presumptive diagnosis of either staphylococcal pneumonia or miliary tuberculosis. Stains for acid-fast bacilli on the sputum were negative. Despite this therapy, the patient's condition deteriorated over the next 48 hours, with progressive respiratory failure, and she underwent an open-lung biopsy. Diffuse involvement of both lungs was noted, with a purulent yellowish exudate. A histologic diagnosis of blastomycosis was made, and a regimen of amphotericin B was started. Despite further intensive efforts, progressive respiratory and renal failure developed, and the patient died on the fifth hospital day. On postmortem examination there was evidence of disseminated blastomycosis with involvement of the lungs, kidney, liver, spleen, skin, left talus, and subtalar joint. Subsequent cultures were positive for *B dermatitidis.*

Case 3

The patient, a 51-year-old woman from Maple Creek who worked part-time as a secretary, was admitted to hospital in December 1982 for excision of a lesion in the left upper lobe. She had been evaluated for mild hypertension a month previously, and the chest radiograph showed a nodule in the left upper lobe. There were no pulmonary symptoms. She had had an appendectomy in 1983, and there was a 46-pack-year history of smoking. A travel and residence history revealed that she had lived in Saskatchewan all her life, with the exception of a one-year residence in Brandon, Manitoba, in 1960 to 1961.

Physical examination and laboratory studies showed no abnormalities. On a chest radiograph there was a well-circumscribed 1-cm nodule in the apical segment of the left upper lobe that had grown by 0.2 cm over the past year. Tomography confirmed the presence of a well-circumscribed nodule with eccentric calcification. A computed tomographic scan of the chest showed either liquefaction or necrosis within the center of the lesion. A thoracotomy was done and the nodule completely excised; on frozen sections there was spherical, thick-walled, budding yeast with broad bases, highly suggestive of *B dermatitidis.* Unfortunately, cultures were not done.

Discussion

Blastomycosis is a chronic granulomatous and suppurative disease involving primarily the lungs, skin, bones, and genitourinary tract.[1,7] Sporadic cases occur more frequently in middle-aged men, but during epidemics no sex predilection is apparent. The portal of entry in humans appears to be the lungs, with the mode of transmission being inhalation of aerosolized conidiophores.[1,6] The usual histologic picture is that of granulomatous inflammatory reaction. In the vast majority of cases, disease found at other body sites is the result of dissemination from an initial pulmonary infection.

Clinical features vary according to the site of involvement.[3,8,9] Acute infection may cause an acute pneumonitis not unlike influenza or bacterial pneumonia or an asymptomatic pneumonitis. From this point, either recovery or progressive disease may ensue, with progressive disease manifesting as either pulmonary or extrapulmonary disease (or both). It is uncertain whether endogenous reactivation may occur. The radiologic findings in the acute stage of disease, whether symptomatic or asymptomatic, are usually of consolidation in either a lobar or segmental distribution. The clinical findings in chronic disease are protean but are characterized by an indolent and progressive course. Although chronic fibronodular pneumonia is most frequent, cavitation,

extraction solvent ("Key Chemicals: Methylene Chloride," *Chemical Engineering News*, 1980, vol 58, p 11). Therefore, the potential exists for methylene chloride exposure from a wide range of environmental sources, from industrial activities, and from the use of consumer products. Methylene chloride readily enters the body through the lungs due to its high volatility. Methylene chloride can also be absorbed through the skin in significant amounts.[9] Methylene chloride is a known hepatotoxin in both humans[10-12] and animals.[13-15] Methylene chloride is metabolized producing carbon monoxide. The production of carbon monoxide is responsible for most of the acute effects of methylene chloride intoxication, and the severity of an acute exposure can be assessed by determining carboxyhemoglobin levels.

Both of the cases presented satisfy the criteria for occupationally induced illness.[16] Our first purpose in presenting them is as a reminder that occupational diseases do not usually present with unique findings that allow easy differentiation from nonoccupational causes. The possibility of an occupational disease can result in both an inaccurate diagnosis and inappropriate treatment. In addition, the patient may be denied the benefits of financial compensation for work-related illnesses.

Second, these cases involve chemically induced hepatitis, a phenomenon whose incidence rate is largely undefined. It may well be that many cases are mild and go unrecognized. Cases involving only mild elevation in liver enzyme levels may be attributed to other factors, including spurious laboratory results. When detected, abnormalities in liver studies should be observed for a return to normal. Laboratory studies providing a more sensitive assessment of liver function include the indocyanine green clearance test,[17] the antipyrine clearance test,[18] and fasting levels of serum bile acids.[19] Workers with confirmed solvent-induced chemical hepatitis may not be able to return to occupations that expose them to hepatotoxic chemicals, as persistent clinical sensitivity will result in the rapid development of hepatitis following reexposure.

The risk of long-term sequelae from transient liver injury is unknown. In the case of methylene chloride, recent data suggest a potential for carcinogenicity in animals.[20] Where a medical surveillance of workers is done, evaluation of hepatic status, including medical and occupational history, physical examination, and appropriate laboratory studies, should be part of the program for workers exposed to known hepatotoxins.

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Blastomycosis in Saskatchewan

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TOM MARTIN, MA
JOHN M. CONLY, MD, CCFP, FRCP(C)
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BLASTOMYCOSIS, caused by the dimorphic fungus *Blastomyces dermatitidis*, is endemic along the Mississippi, Missouri, and Ohio river basins in the United States and in Manitoba, Quebec, and an area north and east of Lake Superior in Ontario.[1-3] The natural habitat of this organism remains a mystery, although it has been isolated from soil on a few occasions.[4-6] Although one case originating in Alberta was reported in 1982, blastomycosis is not known to be endemic to western Canada.[7] We document here three cases in persons who to our knowledge had no significant residence outside Saskatchewan.

Reports of Cases

In reviewing microbiologic records at University Hospital in Saskatoon between 1972 and 1986, we found three cases in which *B dermatitidis* had been identified by either cultural or histologic means. All charts were reviewed, and, when necessary, additional information was obtained by contacting the families or attending physicians or both. Details of travel and places of residence were obtained in all cases.

Case 1

The patient, a 56-year-old power plant mechanic from Saskatoon, was admitted to hospital in March 1973 because of cough and fatigue for eight months. The cough was de-

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scribed as initially nonproductive but later as minimally productive. For the four weeks preceding admission he had hemoptysis, a dull aching left-sided chest pain, nausea, poor appetite, and a weight loss of 3.1 kg (7 lb). His past history was unremarkable except for 40 pack-years of smoking. Detailed travel and residence histories revealed only that he had taken brief holidays to North Dakota two years previously and Wyoming eight months previously.

On physical examination, he was thin and asthenic appearing; the only abnormality found was a perforated right tympanic membrane. Laboratory investigations elicited a hemoglobin of 13.5 grams per dl and a leukocyte count of 14.9 $\times 10^3$ per μl. The chest radiograph showed a mass lesion in the posterior segment of the left upper lobe. Tomograms confirmed the presence of a mass lesion along with complete collapse of the left upper lobe.

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Case 2

The second patient was a 58-year-old woman, a homemaker from Mistatim, Saskatchewan, who had a longstanding history of diabetes mellitus and ischemic heart disease. In September 1980 she was admitted to hospital with a 12-week history of cough, anorexia, weakness, and many small ulcerative skin lesions, some of which were draining purulent debris. She also had pain in the left heel. Ten days before admission to University Hospital, she was admitted to the local hospital with a tentative diagnosis of "bacterial pneumonia," and ampicillin and gentamicin sulfate were administered intravenously. She continued to have cough productive of a thin, mucoid sputum and because of failure to respond was transferred to University Hospital. She had had a tonsillectomy in 1950, excision of a benign intracranial tumor in 1952, insulin-dependent diabetes mellitus since 1964, and degenerative joint disease of the left knee since 1977. A travel and social history revealed that she had been born and raised on a farm near Prudhomme, Saskatchewan, and had moved to Mistatim only five years previously.

On physical examination she was pale, thin, and appeared ill, with tachycardia, tachypnea, and a temperature of 38.9°C (102°F). Many small ulcers, some with purulent drainage, were present on the trunk and extremities. The left heel was tender, with edema of the dorsum and the lateral aspect of the foot. She had oral thrush. There were diffuse inspiratory and expiratory crackles throughout both lung fields. Laboratory studies showed a hemoglobin of 12 grams per dl, with a leukocyte count of 10.9 $\times 10^3$ per μl. Electrolytes and tests of renal function gave normal values. The chest radiograph showed a diffuse reticulonodular interstitial pattern. Initial blood cultures were negative, and sputum Gram's stain and culture revealed abundant pus cells, no bacteria, and a light growth of *Staphylococcus.*

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nodules mimicking carcinoma, and miliary disease have been described. In two of our patients, a presumed diagnosis of bronchogenic carcinoma was made based on the history and radiologic findings. Cavitation had occurred in the third patient. The second patient presented with miliary disease and widespread dissemination with a rapidly progressive course. Mortality has been reported to be 50% or greater in this group.

In chronic extrapulmonary disease, almost any body organ may be involved. The skin and osseous, genitourinary, and central nervous systems are most frequently involved. The onset of chronic pulmonary or extrapulmonary disease in an individual patient represents an interplay of exposure to the fungus, the host, and the host defenses. Our second case represents an immunocompromised host with rapidly advancing and widespread disease with multiple organ involvement. Although *B dermatitidis* may function as an opportunist in some cases, it is generally considered a primary pathogen.

Although soil is the natural habitat of many pathogenic fungi and is presumably the same natural habitat for *B dermatitidis,* this hypothesis has not been well substantiated. A recent study, however, of an outbreak of blastomycosis among school children in Wisconsin on a field trip to a beaver lodge has shown that soil can be a reservoir for *B dermatitidis* and a source of human disease.[6] Soil from which the fungus was isolated had a high organic material content, a low pH, and it was speculated that old animal habitats may be related to the ecology of the fungus. Similarly, *B dermatitidis* has also been isolated from an earthen floor in southwestern Ontario.[10]

In Canada, blastomycosis has been described as occurring in Quebec, Ontario, and southern Manitoba and affecting both the human and canine populations. Blastomycosis has been recognized in dogs in Saskatchewan since 1971, and there have been 14 cases of canine blastomycosis documented from the eastern half of the province since this time (J. R. Saunders, DVM, Department of Veterinary Microbiology, University of Saskatchewan, Saskatoon, oral communication, November 1986). Nine of these cases have originated from the Regina-Moose Jaw area. From available records on 7 dogs, all 7 were native to Saskatchewan.

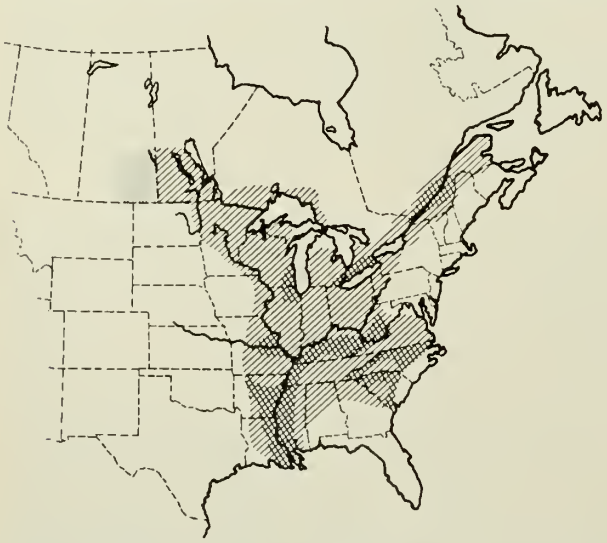

Figure 1.—Endemic regions for blastomycosis in North America. The diagonal line represents the currently recognized endemic regions, the hatched areas represent areas with the highest incidence, and the dotted area represents the newly recognized regions in eastern Saskatchewan.

We report here three human cases of blastomycosis in Saskatchewan. Although two of the three patients resided for a time outside the province, in both, these periods of residence were remote to the onset of illness and were not considered to be related. These three cases represent those seen at only one major tertiary referral center, and it is conceivable other cases may have presented to other institutions. Blastomycosis in the canine population in Saskatchewan, particularly in the eastern half of the province, has been recognized for some time. The geographic and climatic differences between southern Manitoba and Saskatchewan are minimal. Given our expanding knowledge of the ecologic niche of this fungus, the lack of any distinct topographic boundaries between a known endemic region (Manitoba) and much of our province, and the recognized presence of disease in both canine and human populations native to this area, Saskatchewan should be considered (Figure 1) as an "endemic" region for blastomycosis.

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Barium Appendicitis

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FILLING of the appendix following a barium study of the gastrointestinal tract commonly occurs and is thought to be without consequence. Most patients will have spontaneous evacuation of barium from the appendix within 72 hours, though in children this may take up to two weeks.[1] While barium itself is nonirritating to the appendiceal mucosa, retained barium may form a concretion and, much like an appendicolith, obstruct the appendiceal lumen and result in the development of acute appendicitis with its inherent problems.

(Palder SB, Dalessandri KM: Barium appendicitis. West J Med 1988 Apr; 148:462-464)

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We present two cases of acute appendicitis thought to be directly attributable to barium radiographic studies of the gastrointestinal tract.

Reports of Cases

Case 1

A 66-year-old man was admitted to the Urology Service because of urinary retention secondary to a urethral stricture that occurred after a previous transurethral resection of the prostate. In addition to his urologic symptoms, the patient complained of right lower quadrant pain for two hours associated with anorexia, nausea, and malaise. He denied any other gastrointestinal or genitourinary symptoms. His medical history was notable for sigmoid diverticulitis, which was treated medically (Figure 1), bilateral inguinal herniorrhaphies, and benign prostatic hypertrophy. On physical examination the patient was afebrile and in moderate abdominal distress. His abdominal examination revealed tenderness over McBurney's point and voluntary guarding, though no peritoneal signs were present. There was a positive psoas sign on the right. A rectal examination revealed guaiac-negative stool with some point tenderness along the right lateral rectal wall. A leukocyte count showed a moderate leukocytosis (13,500 per μl with slight left shift); the hemoglobin was 18 grams per dl with a hematocrit of 50%. Other laboratory study results were normal. A radiologic study of the kidneys, ureter, and bladder showed multiple retained barium concretions (Figure 2). When compared to the previous barium enema study (Figure 1), it was apparent that these concretions were within colonic diverticula and the appendix. An operative specimen was found to contain barium. An x-ray film of the specimen showed the same barium concretions as seen on the preoperative kidney, ureter, and bladder film (Figure 3). At the same operative setting the patient had an internal urethrotomy done by the Urology Service. Postoperatively, the patient experienced an ileus, which responded to intravenous fluid hydration and bowel rest. He was discharged on the eighth postoperative day. At four months follow-up he is doing well.

Figure 1.—Barium enema study shows multiple diverticula in the sigmoid colon. The appendix easily fills with barium.

Figure 2.—A kidney, ureter, and bladder film shows multiple barium concretions within colonic diverticula and within the appendix.

Figure 3.—Radiographic analysis of the operative specimen shows barium within the lumen of the appendix.

Case 2

A 45-year-old man was admitted to the Surgery Service with a six-hour history of right lower quadrant pain associated with chills, malaise, anorexia, nausea, and emesis. The pain originally was periumbilical in nature. He denied any other gastrointestinal or genitourinary symptoms. His medical history was significant for postprandial epigastric pain attributed to peptic ulcer disease because it had responded to the use of antacids and dietary modification and because an upper gastrointestinal series done six months earlier had been highly suggestive of a duodenal ulcer. On physical examination the patient had a temperature of 38°C (100.4°F) and was in moderate abdominal distress. His abdominal examination revealed persistent peritoneal tenderness over McBurney's point, involuntary guarding, and a questionable mass in the right lower quadrant. A leukocyte count was 17,200 per μl with a left shift, and the hemoglobin was 15 grams per dl with a hematocrit of 47%. Other laboratory study results were normal. A film of the kidneys, ureter, and bladder showed a single barium concretion in the right lower quadrant (Figure 4). The patient was taken to the operating room with a presumptive diagnosis of acute appendicitis. At operation the diagnosis was confirmed—the appendix was acutely inflamed and enveloped by omentum. The operative specimen was found to contain the barium concretion. Postoperatively, the patient made a rapid recovery and was discharged on the fourth postoperative day. At 12 months follow-up he is doing well.

Discussion

It is generally accepted that filling of the appendix with barium and visualization of the entire appendix are reliable signs of a nondiseased appendix, as is seen in 80% to 90% of routine upper gastrointestinal and barium enema studies.[1,2]

Figure 4.—A kidney, ureter, and bladder film shows a single barium concretion in the right lower quadrant.

Spontaneous emptying of the barium-filled appendix occurs within 72 hours in most persons, although it may take up to two weeks in children.[3] While there is no evidence that barium produces an inflammatory response in the appendiceal mucosa, there is good evidence to suggest that retained barium may result in appendiceal obstruction, as with any other appendicolith, with resultant inflammation and perforation. It is well known that in 24% to 45% of cases of acute appendicitis and 52% to 86% of cases of perforated appendicitis, there is documented evidence of an appendicolith.[4,5] These cases of gangrenous and perforated appendicitis have an increased incidence of postoperative morbidity. There is every reason to consider retained barium within the appendix of a symptomatic patient in the same vein as any other appendicolith.

Some authors have suggested that all persons with prolonged appendiceal retention of barium should undergo an interval appendectomy; others have advocated follow-up kidney, ureter, and bladder films at routine intervals.[6] We think that the presence of retained barium within the appendix should be regarded as having the same importance as any other appendicolith, carrying a high risk of gangrene and perforation, and we advocate early appendectomy in symptomatic patients with evidence of retained barium within the appendix.

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Splenic Pseudocysts—Diagnosis and Management

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SIMPLE SPLENIC CYSTS, in contrast to cysts involving other abdominal viscera, are relatively uncommon. They can be classified as true or false cysts depending on whether they have an epithelial lining.[1] True cysts can be either congenital[1,2] or parasitic; false cysts or pseudocysts originate from traumatic, degenerative, or inflammatory processes and can be quite large at presentation.[2] Although these pseudocysts may be asymptomatic when they are initially found, their natural history and differential diagnosis have important im-

(Gibeily GJ, Eisenberg BL: Splenic pseudocysts—Diagnosis and management. West J Med 1988 Apr; 148:464-466)

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plications for the surgeon. For the purpose of evaluating this uncommon problem and reviewing the literature, we present two cases of splenic pseudocysts.

Reports of Cases

Case 1

The patient, a 24-year-old woman, was given a routine examination. She had been completely asymptomatic and her medical history and physical examination results were both unremarkable. Laboratory data were normal with the exception of her chest and abdominal x-ray films. These showed an 8 × 9 cm calcified mass in the left upper quadrant. An ultrasound study confirmed the presence of a 7-cm splenic cyst with an echogenic region in the most dependent portion. Echinococcal titers were negative. There was no history of abdominal trauma. An exploratory laparotomy revealed a whitish, firm cystic mass on the superior medial aspect of the spleen. The mass was adherent to the inferior aspect of the left hepatic lobe and the diaphragm. A splenorrhaphy was done, with excision of the cyst wall and placement of omental packing. On gross examination, the cyst measured 6.5 cm in greatest diameter and contained a yellowish, clear fluid, with no evidence of echinococcal scolices. On final pathologic study, the cyst was found to be consistent with a simple calcified pseudocyst.

Case 2

The patient, a 20-year-old woman, presented with an upper respiratory tract infection of four weeks' duration associated with dizziness, bloating, and left upper quadrant pain that increased when she lay on her left side. She had a history of nonspecific abdominal trauma at an early age. Her medical history was otherwise noncontributory. Physical examination revealed a soft and painless mass in the left upper quadrant. Laboratory data were completely normal. A technetium scan indicated a central splenic lucency compressing a rim of the spleen (Figure 1). A computed tomographic (CT) scan showed a simple, large cystic mass of the spleen occupying approximately 90% of the parenchyma (Figure 2). At laparotomy the patient was found to have a 10 × 11 × 12 cm splenic cyst containing clear, yellowish fluid. An accessory spleen was left intact at the splenic hilum. Splenectomy was done, and pathologic study revealed a spleen weighing 258 g, measuring 10 × 11 × 9 cm with a central unilocular cyst 8 cm in diameter. The cyst had no epithelial lining and was, therefore, consistent with a pseudocyst.

Discussion

The primary cause of splenic pseudocysts is either recent or remote trauma.[2] This can result in a subcapsular hemorrhage or a splenic hematoma, and if early rupture does not occur, then liquefaction and formation of a fibrous capsule can result. Absorption of the products of liquefaction causes a residue of serous fluid, cholesterol crystals, and fat-laden mononuclear cells.[3,4] Roberson reported a 0.05% incidence of splenic cysts in his examination of 800 spleens after splenectomy.[5] This incidence could certainly increase as splenic preservation following traumatic injury is more common. These cysts often occur in the second or third decade of life. They have been noted in greater frequency in women, suggesting a possible association with menstruation or pregnancy.[6]

The symptoms related to splenic cysts are varied and result from displacement and compression of neighboring organs,[7] as was true of our second patient. Occasionally, these patients can suddenly become symptomatic following a minor trauma that is sufficient to cause an increase in size by hemorrhage into the cyst.[7] Patients with splenic cysts may have symptoms ranging from early satiety and constipation to dysphagia, vomiting, and weight loss.[6,7] The symptoms can be exacerbated by certain positional changes. Upward

Figure 1.—A technetium Tc 99m-sulfur colloid liver-spleen scan shows a splenic cyst.

Figure 2.—An abdominal computed tomographic scan shows a large, central splenic cyst.

pressure on the diaphragm has been reported to cause pleuritic pain, dyspnea, lower lobe atelectasis, and recurrent pneumonias.[8] The most immediate and life-threatening problem associated with a splenic pseudocyst is spontaneous rupture, which occurs in about 25% of cases.[9] A patient with a ruptured splenic pseudocyst presents with hemoperitoneum and shock and requires immediate surgical intervention. For this reason it is advisable to remove these cysts at the time of diagnosis, even in an asymptomatic patient.

Differentiating splenic cysts from other intraabdominal visceral cysts can sometimes be difficult. The differential diagnosis would include omental and mesenteric cysts, as well as cysts of the left kidney, liver, pancreas, left adrenal gland, and left ovary. Ultrasound study, computed tomographic scan, and liver-spleen scan are all helpful in making the diagnosis. Routine abdominal radiographic films may detect splenic cyst calcifications; however, these may be difficult to distinguish from splenic artery aneurysms.[8]

If a patient has a history of exposure to an animal carrier or has lived in areas where echinococcosis is endemic, it is necessary to consider echinococcal infection. This infection can result in the formation of splenic cysts similar in appearance to pseudocysts; injury to such cysts during laparotomy may cause intraabdominal dissemination of echinococcal scolices. Echinococcal cysts of the spleen generally arise on the upper pole and if calcified, the rim tends to be less dense and incomplete compared to nonparasitic cysts.[4] If echinococcal cysts are suspected, a serum complement fixation test can be helpful.[1]

There is some controversy regarding the treatment of splenic cysts. Recommendations range from simple observation to splenectomy. In 1950, Fowler popularized splenectomy as the treatment of choice, reporting a minimal mortality rate.[1] With further evidence of the spleen's role in immunosurveillance, there has been an increasing emphasis on splenic salvage, especially in pediatric patients. Cyst excision or splenorrhaphy can be considered if the cyst does not involve the splenic hilum and if there is a major division in the extrasplenic blood supply.[10] Partial cyst excision and marsupialization is another option. The two patients in our series had large splenic pseudocysts. In one patient a cyst excision was done and the spleen salvaged. In the other the cyst occupied a large portion of the spleen, and its position in the splenic hilum necessitated splenectomy. It would be prudent, however, to attempt splenic preservation when feasible either by splenorrhaphy, cyst excision, or drainage and marsupialization.

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Acute Renal Failure Due to Rhabdomyolysis Associated With Cocaine Toxicity

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ACUTE RENAL FAILURE due to rhabdomyolysis has been reported with the use of amphetamines, heroin, and phencyclidine hydrochloride. Despite the recent upsurge in popularity of cocaine as a "recreational drug," however, there has been no report of myoglobinuric renal failure associated with cocaine abuse. We describe the case of a patient in whom rhabdomyolysis and renal failure developed after numerous intranasal doses of cocaine over several days. The clinical aspects of this case are similar in many respects to those of rhabdomyolysis associated with phencyclidine or amphetamine abuse.

Report of a Case

A 33-year-old, previously healthy man was admitted for bizarre behavior and fever. The patient was noted to be increasingly despondent recently. He had been a cocaine user "off and on" for about ten years. During the three days before admission he began using 10 to 14 grams of cocaine intranasally daily. Subsequently he became very agitated and delirious. He locked himself in his room, refusing to communicate with his family or to eat or drink. In the night before admission to hospital, the patient was reported to be yelling, barking, and running into the walls.

Physical examination revealed a temperature of 40°C (104°F). The blood pressure was 140/90 mm of mercury with a pulse rate of 120 per minute and a respiratory rate of 32. The patient was severely agitated and had babbling speech. At times he required restraints, yet he was alert and oriented. Multiple ecchymoses were present throughout his body. Laboratory data included a serum creatinine value of 2.5 mg per dl, blood urea nitrogen of 26 mg per dl, and the initial creatine kinase was 514 IU per liter. The serum calcium was 7.0 mg per dl and serum albumin, 3.3 grams per dl. Serum phosphate was 3.8 mg per dl and the potassium was 4.7 mmol per liter. The leukocyte count was 18,400 per μl with 76% granulocytes, 18% lymphocytes, and 6% monocytes reported by the automated cell differentiator. The hematocrit level was 48% with a hemoglobin concentration of 16.3 grams per dl. A urinalysis showed a moderate amount of ketones and 4 to 10 granular casts per high power field. Initially the dipstick revealed no blood, but subsequently it did so in the absence of microscopic hematuria. Urine myoglobin was present in a concentration of 11.9 μg per ml. Urine and blood toxicology screens confirmed the presence

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of cocaine as well as of its urinary metabolite, benzoylmethylecgonine. No other drugs were identified.

Therapy consisted of vigorous intravenous fluid replacement, 25 grams of mannitol, and sedation with diazepam (Valium) and haloperidol (Haldol). The patient remained nonoliguric; however, on the second hospital day, the serum creatinine level peaked at 3.9 mg per dl and the blood urea nitrogen at 34 mg per dl. The serum creatine kinase reached a peak of 57,300 IU per liter (normal range, 16 to 195) with 98.2% MM fraction on isoenzyme determination. Clinically the patient improved rapidly. His fever subsided and his agitation abated. He was discharged on the fourth hospital day with a serum creatinine value of 2.7 mg per dl and a blood urea nitrogen concentration of 17 mg per dl. Unfortunately, the patient was lost to follow-up.

Discussion

Cocaine, an alkaloid derivative of the plant *Erythroxylon coca,* has long been used for medical and cultural purposes. Recently the use of cocaine as a stimulant and euphoric agent has greatly increased. With its popularity, there have been many reports of various complications associated with cocaine toxicity. Acute myocardial infarction, with and without atheromatous coronary artery disease,[1-5] ventricular dysrhythmias,[6] renal infarction,[7] bowel ischemia and infarction,[8,9] pulmonary dysfunction,[10] and subarachnoid hemorrhages[10] have thus been reported. Rhabdomyolysis with acute renal failure, however, has not been previously associated with cocaine intoxication. Nontraumatic rhabdomyolysis and acute renal failure have been reported in association with a number of commonly abused drugs.[12,13]

Rhabdomyolysis seen in association with heroin and barbiturate abuse is probably related to local pressure necrosis from the patient's own body while the patient is obtunded or unconscious.[14] Rhabdomyolysis has also been associated with phencyclidine use.[15-17] This has been postulated to be due to muscle damage caused by the use of restraints in a hyperactive, combative patient.[16] Others have proposed that the acute dystonic reaction induced by phencyclidine caused the muscle damage.[17] Amphetamine abuse has also been associated with rhabdomyolysis and acute renal failure.[18-20] Hyperpyrexia and increased muscular activity seen in these patients have been considered important in causing the muscle damage.[19] Cocaine is unique among the local anesthetics in its ability to enhance the effects of sympathetic stimulation. The action of epinephrine and norepinephrine is terminated with the uptake of these drugs at the adrenergic nerve endings. Cocaine blocks this uptake, thus prolonging the effects of catecholamines. Cocaine also facilitates norepinephrine release, activates tyrosine hydroxylase, and produces an increased β-receptor density. With ongoing use, both α- and β-receptor sensitivity is increased.[21,22] Consequently, with cocaine toxicity, features of sympathetic overactivity appear, such as dilated pupils, tachycardia, hypertension, and intense vasoconstriction.[23] Cardiac lesions found in cocaine abusers are histologically similar to those seen in patients with excess catecholamine stimulation, as in those who have pheochromocytoma or have received large amounts of catecholamines during a cardiopulmonary resuscitation.[24] In the central nervous system, cocaine initially acts as a stimulant and then as a depressant. This central stimulation, as well as a cocaine-induced elevation in circulating catecholamines, leads to increased motor activity, which initially is well coordinated. When lower motor centers are affected, however, uncontrolled tremors and convulsive movements may result.[21] This increase in motor activity with a concomitant vasoconstriction that decreases heat loss may result in hyperpyrexia.

In the case described here the elevated serum creatine kinase (57,300 IU per liter) and the myoglobinuria (11.9 μg per ml) support the diagnosis of rhabdomyolysis. The intranasal doses (10 to 14 grams per day) reportedly taken by this patient before admission are extremely high when compared to the 1 to 32 grams per week range given in the national survey of the National Institute on Drug Abuse by the 800-COCAINE helpline callers.[22] As a chronic user, our patient may have been more sensitive to the sympathomimetic effects of his cocaine binge preceding admission.

Several possibilities may account for rhabdomyolysis in association with cocaine consumption in this patient. It is possible that the sympathetic overactivity resulted in vasoconstriction. The vasoconstriction in the setting of muscular overactivity may have resulted in microinfarctions with skeletal muscle necrosis. Hyperpyrexia with fluid losses and inadequate replacement may have also participated in the end result of acute renal failure. Alternatively, cocaine intoxication is known to cause seizures.[25] It is possible that while locked in his room the patient may have had unobserved seizures as the cause of rhabdomyolysis.

Phencyclidine-related rhabdomyolysis may be more likely to occur in the case of a hyperactive patient who is placed in restraints. The patient described here was agitated and required restraints at times; however, the need for restraints was not a major part of his clinical course, as so often is the case in patients intoxicated with phencyclidine. We certainly could not exclude traumatic rhabdomyolysis as a cause of his muscle damage. His history of running into the walls of his locked room and multiple ecchymoses on his body support the possibility of traumatic rhabdomyolysis. He did not, however, have obvious areas of myoedema or massive ecchymosis. Finally, the possibility that large doses of cocaine may have a more directly toxic effect on skeletal muscle in vivo cannot be excluded. Catecholamine excess seems to cause myofibrillar degeneration in humans and experimentally in animals.[26] More recently, investigators have described similar changes in myocardial muscle of cocaine abusers.[24] The initial negative finding of the benzidine urine dipstick at a time when the creatinine concentration was already elevated is compatible with rhabdomyolysis-associated acute renal failure. Creatinine often has an initial rapid rise due to the release of creatine from damaged muscle and its subsequent conversion to creatinine. Creatine kinase levels, on the other hand, usually peak on the second or third day, followed by a decline of 50% every 48 hours.[27] It is thus a more sensitive indicator of rhabdomyolysis than the presence of myoglobinuria. The absence of myoglobinuria in many cases of rhabdomyolysis-associated renal failure may suggest that other nephrotoxic products are released from muscle or, alternatively, that myoglobin excretion may be brief[27] and intermittent in view of the varying glomerular filtration rate and perfusion to damaged muscles.

The above case represents an association of cocaine intoxication and rhabdomyolysis with myoglobinuric renal failure. It has similarities with amphetamine- and phencyclidine-associated rhabdomyolysis, which also induce sympathetic overactivity. We report this case to draw attention to the

potential risk of rhabdomyolysis in cocaine intoxication. Further reports and studies may define the incidence and circumstances of occurrence of this additional deleterious effect of cocaine abuse.

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Correspondence

Tricyclics and Child and Adolescent Suicides

To THE EDITOR: A special team reviews all child deaths potentially related to maltreatment in our county. As part of that work, we examine the child and adolescent suicides.

In the past year, we have seen two teen deaths from overdoses of tricyclic antidepressants. The team has asked me to point out to the medical community the caution necessary in the use of these drugs.

Tricyclics clearly have value in the treatment of some forms of adolescent depression. They are also used to treat enuresis in childhood, and, at times, the attention deficit disorder/hyperactivity/conduct disorder syndrome. Unfortunately, the drugs can be lethal when taken in overdoses of relatively modest quantities.

Several options are available to the clinician. He or she can prescribe the drug in small amounts with frequent renewals or can prescribe the drug in a larger amount and arrange with a pharmacist to only dispense a week's supply at a time. The third alternative is to have the parent control the dispensing of the drug. This technique may be ineffective unless the parent is specifically informed as to the potentially lethal consequences of an overdose, and the parent is then able to actually keep the drug inaccessible to the teenager. Some parents have difficulty accepting the fact that their teenager might be suicidal because this is so anxiety-provoking. The prescribing physician needs to take this into account in working with the family.

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Substituting of Generic Drugs

To THE EDITOR: Currently Medi-Cal, health maintenance organizations (HMOs), and independent practice associations (IPAs) are mandating the substitution of generic preparations where the brand name drug has previously been in use by the patient.

As a neurologist, I am concerned about this practice where anticonvulsant medications are concerned. Because there is no proof of the equivalency of a generic anticonvulsant to the brand name drug or, for that matter, to other generic preparations of the same drug, any change from the preparation with which seizure control was obtained must be viewed as a therapeutic trial and, as such, one attended by the slight but real possibility that seizure control could be lost.

Such is the case in changing patients with Dilantin-induced gingival hypertrophy from an optimal Dilantin dosage to an optimal Tegretol dosage. It must be conceded to the patient that, while these two drugs are nearly equivalent in their antiepileptic potency, nonetheless, it is a change that is being made—one that could be attended by less than the complete seizure control that had attended the use of the previous specific drug.

No pharmacy should substitute one anticonvulsant preparation for another—not a generic for a brand name drug or one generic for another—without notifying the prescribing physician. Full disclosure would then be due the patient or, in the case of a minor, the family, before initiating the change. The patient or family would then have the opportunity, as is only appropriate, to consent to or reject the proposed change with the risk that the change entails. Clearly, whenever substitution of a drug that is not the proved equivalent of the product previously used is contemplated, there exists an ethical and practical need first to notify the prescribing physician, so that he or she in turn can apprise the patient or the patient's family and thus proceed or not proceed, whichever is their decision, after full disclosure.

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Categorization and Regionalization of Health Care

To THE EDITOR: I, too, commend Dr R. Myles Riner and colleagues for their much needed work on "Categorization of Hospital Emergency Services" as reported in the November 1987 issue.[1] I do, however, take issue with Dr George Trager's comments in the correspondence section of the January 1988 issue.[2] I do not believe that we are all "jumping to the tune of categorization," since the processes of categorization and also regionalization of care have been studied for some time with many studies demonstrating improvements in morbidity and mortality.[1,3] In fact, the many recent studies on trauma care as outlined by Cales and Trunkey[3] clearly demonstrate the value of categorization in just one of many areas—trauma centers. I am, therefore, in strong disagreement with the statement by Dr Trager that "no one has demonstrated that for all its cost and trouble, categorization really saves lives and reduces morbidity." Dr Trager's point that categorization involves a lot of work is true, but it will result in improved, cost-effective patient care, as substantiated in the literature cited.

I believe that the demands that the state or local agencies place on hospitals and physicians in the area of categorization and regionalization are justified. If the medical communities could settle their own differences ("turf" wars and so forth), and apply the scientific body of knowledge available to us in designing regional protocols, the governmental agencies would not have to impose upon the medical communities. Therefore, although a certain degree of "bureaucracy" will be generated by the new system, it can be kept to a minimum by keeping medical control within the community if the physicians act in a responsible and timely fashion.

Last, Dr Trager indicts the "inept" local emergency medical services (EMS) agency and the fact that "not one shred of evidence has been published to date" demonstrating the efficacy of their trauma system. If the EMS agency is inept and if no data have been published from this area, this does not invalidate the concepts of categorization or regionalization but only serves to demonstrate that an adequate program has not been implemented in that particular area.

Categorization and regionalization of all care are concepts that must be implemented into contemporary health

policy, because they improve patient care in a cost-effective manner. The medical community must take the timely initiative to implement and control such programs before other agencies impose them upon us.

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Obstructive Sleep Apnea

To the Editor: While there is much sound advice in Dr Eliot Phillipson's editorial on the treatments for obstructive sleep apnea,[1] there is obvious bias against surgical management and the implication that haphazard (his word is "unselected") application of uvulopalatopharyngoplasty and other operations results in a 50% cure rate and unspecified irreversible consequences.

Elsewhere he states (and I agree) that treatments for sleep apnea have not been subjected to rigorous clinical trials. Unfortunately for his readers, he neglects to mention first that such studies have been and continue to be attempted and have failed because one half of all postoperative patients refuse a follow-up sleep study because of symptom improvement. Is this entirely a treatment placebo effect, as Dr Phillipson implies? I doubt it. I suspect, as does Dr Phillipson, that while polysomnography is the best diagnostic tool now available, the results do not always correspond with the clinical symptoms. Whom are we to believe in such cases, the patient or the machine?

I also take issue, on the basis of my clinical experience, with his assertion that a regimen of weight loss, avoidance of sedatives, modified sleeping position, and (sometimes) protriptyline is a common successful approach to the management of these patients. It sounds good on paper, but in patients with more than minor problems, it is ineffective. Continuous positive airway pressure (CPAP), on the other hand, is effective and worthwhile.

In my view as a surgeon with considerable experience in the management of patients with obstructive sleep apnea, the pro and con arguments about which treatment is better, CPAP or surgery, truncates to two decisions by the physician: Is each patient fully informed about the alternatives, including no treatment? Are there anatomic or other factors that, in the physician's opinion, materially affect that patient's consent? It would seem from Dr Phillipson's editorial that his patients are not so managed. I, personally, would not choose to spend the rest of my life sleeping with a bag on my nose.

On the basis of such editorials and what I have been told by other physicians, there seems to be a turf battle developing once again between medical and surgical management, with patients getting less information than they deserve on their alternatives. In past times both disciplines worked together effectively. I would like to see the team continue towards some real solutions beyond those that are 50% or 75% effective.

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Strike! From the Other Side

To the Editor: Dr Elliott Wolfe's article in the January issue[1] only needed Peter Pan and Tinker Bell to complete its naiveté. I can't believe that he was running around the hospital having such a good time scabbing against the members of the Hospital Institutional Workers Union—enjoying himself without having a single thought about the salaries paid for the jobs that he was doing and for the reason behind the strike. Nor was there a single comment about the seven weeks the strikers went without salaries.

Perhaps he should sit down and take a close look at the circumstances surrounding the employees with whom he works and who serve the patients and the physicians of the Kaiser Hospital system and see if he can find a little more depth and meaning to "Strike!"

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Subspecialty Differences in Responding to Patient Death—Comparing Cardiologists With Oncologists

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Cardiac deaths are more likely to be unanticipated than cancer deaths by patients, their families, and their physicians. We hypothesized that differing physician attitudes toward dying patients may affect the degree of expectation of death. To evaluate differences in attitudes and behaviors among subspecialists, we surveyed a randomly selected population of California subspecialists; 44 of 136 (32%) of cardiologists and 91 of 167 (55%) of oncologists responded. Oncologists experienced three times as many deaths as cardiologists and reported having discussed code status more often with patients who died. Cardiologists' patients' deaths were more often unexpected and occurred more frequently in intensive care units. In addition, their patients were more likely to be given cardiopulmonary resuscitation. Oncologists reported being more comfortable dealing with dying patients and having less desire to avoid them. When presented with patient scenarios, however, cardiologists' and oncologists' responses were similar when discussing and estimating prognosis and likelihood of successful therapy.

(Bates DW, Tolle SW, Elliot DL: Subspecialty differences in responding to patient death—Comparing cardiologists with oncologists. West J Med 1988 Apr; 148:471-473)

Unexpected deaths are often traumatic for family members, who are more likely to have poor subsequent adjustment than when a death in the family is anticipated.[1-3] Data from interviews with survivors of patients who died in 1983 at the Oregon Health Sciences University Hospital document marked variation in the frequency with which death was expected.[1] Physicians and families expected 90% of cancer deaths, but only 40% of cardiac deaths.

We hypothesized that there may be differences in attitudes and practices of cardiologists and oncologists toward dying patients that may affect a survivor's expectation of death. Do the two subspecialties estimate or discuss prognosis differently? To investigate this question, we surveyed practicing physicians about their attitudes and practices regarding patient death.

Methods

We surveyed a random sample of 250 cardiologists and 250 oncologists from the California Medical Association's list of all cardiologists (n = 786) and oncologists (n = 730), including both Association members and nonmembers. Nonrespondents were called, and those belonging to surgical subspecialties or with no listing were eliminated. To follow up on responses from the first survey, a second questionnaire was mailed to all physicians in active practice who had responded to the first questionnaire.

The first questionnaire was composed of 19 questions. The first 5 assessed demographics and the nature of each physician's practice. The next 10 addressed the number of patient deaths per physician, whether or not they were expected, where they occurred, and various behaviors by physicians around the time of death. Physicians were also asked whether they had any formal training in death management.

We also presented four patient scenarios: two patients with cancer and two patients with cardiac disease. The prognoses were matched for the four ill patients. A patient with New York Heart Association class IV congestive heart failure and an ejection fraction of 14% was compared with a patient with a locally invasive esophageal cancer. Each disease had a 50% one-year survival.[4,5] The other patient had coronary disease and had had triple coronary artery bypass grafting with an ejection fraction of 30%. This scenario was matched with one with a patient with a Dukes' C colon carcinoma. The literature suggests that both had a 50% survival rate of four years.[5,6] For each scenario, physicians were asked the following:

- Make an estimate of the patient's prognosis, with endpoints of six months and five years;
- State how clearly you would share the prognosis, from not at all—avoiding discussion of prognosis—to giving actuarial prognosis;
- Predict how likely it is that additional therapy would benefit the patient, from no chance of increasing life span to definitely increase life span.

Attitudes were further assessed in the second questionnaire by asking physicians to respond to 13 attitude statements. A visual analogue scale was used with end points of "agree strongly" to "disagree strongly."

Student's *t*-test was used to assess the significance of differences in questionnaire responses between the two groups. Statistical significance was set at the $P < .01$ level.

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Results

Following two mailings, responses were received from 189 of 500 physicians (38%). Of these, 54 belonged to other specialties or were returned without response, leaving 135 respondents: 44 cardiologists and 91 oncologists. After eliminating physicians with no listing and those practicing other specialties from the denominator, our response rate was 32% for cardiologists (44 of 136) and 55% for oncologists (91 of 167). More oncologists than cardiologists responded to the initial questionnaire ($P > .001$, χ^2 statistic). Of physicians who completed the first questionnaire, 79% responded to the second, 74%, cardiologists and 81%, oncologists. Responding cardiologists and oncologists were similar with respect to age, sex, and percentage of time spent in their particular subspecialty.

Demographics of patient deaths were significantly different between the groups (Table 1). Oncologists reported three times as many deaths within the last year as cardiologists. Cardiac deaths were more likely than cancer deaths to be regarded as unexpected. Location of deaths also differed in that only 5% of oncology patients as opposed to 40% of cardiology patients died in intensive care units; many more cancer patients died on hospital wards or at home.

TABLE 1.—*Demographics of Patient Deaths**

Patient Group	*Cardiologists, n=38*	*Oncologists, n=84*
Patient deaths (No./year)	14±2	37±3†
Expected (% total deaths)	63±5	90±1†
Unexpected (% total deaths)	37±4	10±1†
Intensive care unit (% total deaths)	40±4	5±1†
Wards (% total deaths)	37±5	56±3†
Home or nursing home (% total deaths)	22±3	41±3†

*Data are mean ± standard error of the mean.
†$P < .001$.

TABLE 2.—*Behaviors With Respect to Patient Deaths**

Frequencies of Physician Action (% total deaths)	*Cardiologists, n=38*	*Oncologists, n=84*
Cardiopulmonary resuscitation	56±2	15±2†
Do not resuscitate order	42±4	84±2†
Discussed code status	57±3	82±2†
Sent card	33±6	43±4†
Attended funeral	14±3	9±1†
Office appointment	27±4	22±3†
Called or visited family	44±6	42±4†
Autopsies	26±3	20±2†

*Data are mean ± standard error of the mean.
†$P < .0001$.

Management of dying patients differed between the two subspecialties (Table 2). Oncologists more often discussed code status with patients and wrote more "do not resuscitate" orders than did cardiologists. Fewer cancer patients received cardiopulmonary resuscitation. However, no significant differences were observed in the frequency of contact with families following deaths. Several modes of contact were evaluated. Both groups sent cards to 40% of families, went to 10% of funerals, scheduled office visits with 23% of families, and called or visited 43% of the families following the death. Virtually all physicians were available if the family called with questions. Of both groups, 67% reported having had formal instruction in death management. Frequency of requesting autopsies was also similar between the two groups.

Attitudes were evaluated by asking physicians to rate 13 attitude statements on a 10-point scale; several examples are given in Table 3. Oncologists reported being more comfortable in dealing with dying patients and wondered less often if they could have done more to prolong their patients' lives. Cardiologists more frequently found caring for dying patients unpleasant, and stated more often that they might avoid a patient dying from an irreversible condition. The groups' responses were similar, however, when asked whether they would avoid telling a patient that he or she was dying when the patient did not ask. In two other questions asking physicians how clearly they would define prognosis, there was no significant difference between cardiologists and oncologists (data not shown).

Physicians' views on discussing prognosis with a patient were also evaluated with the case scenarios. The cardiologists and oncologists gave similar prognoses and indicated a comparable degree of willingness to share prognostic information with patients (data not shown). Respondents gave similar estimates of the likelihood of success of additional therapy, other than that already received. There was also no systematic difference in physician estimates of prognosis between disease types (cancer versus cardiac) for either of the paired scenarios.

Discussion

We found that the demographics of and attitudes toward patient death differed significantly between practicing cardiologists and oncologists. Cardiologists experienced fewer patient deaths overall than oncologists but regarded many more of these deaths as unexpected. These differences were reflected in the actions of the physicians at the time of death. Cardiologists discussed code status less often and had fewer patients who were classified as Do not resuscitate. Cardiac deaths were eight times as likely as oncology deaths to occur in intensive care units. The predominant attitudinal difference

TABLE 3.—*Attitudes Regarding Patient Deaths**

Survey Statement‡	*Agreement With Statements*	
	Cardiologists, n=28	*Oncologists, n=66*
I feel as comfortable with dying patients as with other types of patients	4.9±.5	2.3±.3†
When patients of mine die, I usually wonder if I could have done something to prolong their lives	3.9±.6	6.1±.3†
Caring for dying patients is one of the unpleasant aspects of my profession	4.4±.5	6.6±.3†
When possible, I avoid a patient who is dying from an irreversible condition	7.0±.5	8.7±.2†
When patients do not ask specifically, I avoid telling them that they are dying	5.0±.5	4.6±.3

*Data are mean ± standard error of the mean.
†$P < .0001$.
‡Each statement had a visual analogue scale from strongly agree (0) to strongly disagree (10) with neutral (5) in the center.

between the groups was that oncologists reported that they felt more comfortable with dying patients and found caring for them less unpleasant.

Our findings provide insight into how two groups of practicing subspecialists approach the death of a patient. The oncologists in our survey experienced a higher number of patient deaths per year and were more comfortable with dying patients than cardiologists but related prognosis similarly. Other studies have found that physicians with a high likelihood of contact with dying patients are more open with them.[7,8] In addition to practice characteristics, physicians' traits may also influence their attitudes toward dying patients. Investigators have suggested that some physicians choose specialties to decrease the likelihood of contact with dying patients.[9,10] Oncologists, on the other hand, may choose their specialty partly because they find rewards in dealing with dying patients.

An unexpected finding was that the group of physicians responding to this survey had substantially more follow-up contact with survivors and more formal death education than has been reported in the literature. In a previous study at our hospital, only 36% of surviving spouses of inpatient deaths had any subsequent contact with their physicians regarding their spouse's death.[1] In a 1983 survey of primary care physicians in Oregon, less than 10% reported routinely sending a card to survivors.[11] The physicians in this study sent sympathy cards 40% of the time and nearly half subsequently called or visited the family. Also, in a 1981 survey of physicians in the Texas Medical Association, less than 10% reported having taken a course on death or dying, while in our survey, 67% of physicians reported some formal instruction in death management.[12]

Although our initial hypothesis was that cardiologists might consistently overestimate longevity in patients with advanced cardiac disease, our data suggest that this is not the case. When presented with patient vignettes, both cardiologists and oncologists clearly identified patients with advanced cardiac disease as having shortened life spans. Cardiac events are commonly episodic, while cancer tends to progress gradually. Despite having patients with disease profiles that are different, the approach of these practitioner groups toward prognosis is remarkably similar. A substantial difference in attitude between cardiologists and oncologists, however, is that oncologists are more comfortable with dying patients. This might reflect experience gathered from their frequent exposure to dying patients or self-selection in choice of specialty.

The degree of expectation of death influences physicians and family members. Families of patients adjust less well after unexpected deaths, and both survivors and physicians experience significantly more stress when a patient dies unexpectedly.[1,13] Following an unexpected death, physicians are more likely to wonder if they should have done something different to have prevented the patient's death.[13] A clear acknowledgement of prognosis may be beneficial for both families and physicians. Increased knowledge about physicians' attitudes and practices in responding to patient death may suggest further options for intervention in this area.

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Medicine in Perspective

Mayan Indian Health in Guatemala

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Opportunities abound for those seeking professional challenge and adventure in novel health care settings. Few Third World countries provide so felicitous a combination of health service needs and an environment of stunning beauty as Guatemala. In the mountainous highlands of its Sierra Madre range the Mayan Indians were our patients. It was in the region of Sololá overlooking Lago Atitlan (the most beautiful in the world according to Aldous Huxley) that we found some unique professional experiences. At the same time we had the opportunity to explore a country richly endowed with magnificent alpine scenery and the artifacts and unchanged life-styles of an ancient Indian culture.

Guatemala's morbidity and mortality data are not unlike those of other Third World countries. Infectious diseases and malnutrition exact a high toll among the poor, especially those without land of their own. Although death rates fell from 35 per 1,000 at the turn of this century to 12 to 15 per 1,000 in recent years, this reduction is not shared equally among all socioeconomic groups. Mean life expectancy is 60 years. For the Mayan Indians it is at least 10 to 15 years less.

High infant and childhood death rates account for the majority of deaths—35% of all children die before the age of five. Poor reporting practices explain variations in mean infant death rates from 60 to 90 per 1,000 live births. For the Indians this death rate may be as high as 100 to 150 per 1,000 live births. Enteric diseases, influenza, respiratory ailments, and measles are the principal causes. The disparity between rural and urban Guatemala is dramatic. Potable water, for example, is available to 87% of city dwellers but to only 15% of rural inhabitants. The latter have almost no sewers.

Early mortality is higher in bottle-fed infants and lower in breast-fed. After weaning from the breast, however, mortality rates rise again, undoubtedly because of the loss of maternal antibodies and the replacement of breast milk with far less adequate nutrition.

In 1985 there were 3 physicians, 2 nurses, 8 technicians, and 22 hospital beds per 1,000 people, with the greatest concentration in the capital, Guatemala City. With 20% of the total population, this city has 80% of the nation's physicians and more than 40% of its dentists, nurses, and laboratory technicians. Public health and social welfare expenditures are three times as high as in the rest of the country. An almost total emphasis is placed on curative medicine, which receives 80% of the health budget. The Highlands region, with its concentration of Mayan Indians, is largely ignored in health planning.

In 1985 we worked in Sololá's two hospitals, gaining an intimate view of health care programs in a small city. We made daily morning rounds in the government hospital with a small staff of established practitioners and recent medical school graduates assigned to fulfill a public service requirement in return for a free medical education.

It became clear why beds were occupied largely by the terminally ill or by those without the alternative of free care. Inhospital services were severely hamstrung by unrepaired equipment and a central pharmacy poorly supplied by the Ministry of Health in the capital. From numerous local sources we confirmed that adequate budgetary appropriations for public health facilities exist only in Guatemala City. In Sololá's much smaller, church-supported hospital served by the same physicians in a private practice setting, underutilization also exists in spite of very modest charges. With few sources of cash that are often inadequate to meet family needs for food, the impoverished Indians have too little to spare for health care. On the other hand, indigenous health providers, the *curanderos,* are often consulted on a barter basis. The extent to which native healers are used is difficult to measure. What was made clear by those with whom we worked is that a deep fund of distrust and resentment of Sololá's medical community has been generated by what Mayans see as two separate and unequal systems of health care, one private, the other public. On the basis of these observations we proposed to our hosts, the local diocese of the Catholic church, that we return the following year to work exclusively in the more remote villages of the Highlands, its *pueblos, aldeas,* and *caserios,* all of which are little more than clusters of the most primitive one-room shelters without any health care facility.

Thus, in December 1986 we returned to Sololá, a city of some 5,000 inhabitants perched 8,000 feet above Lake Atitlan (Figure 1). From our spartan quarters we had a view of the lake and its three symmetrically pyramidal volcanic

Figure 1.—The city of Sololá and Lake Atitlan, Guatemala.

(Minkowski WL: Mayan Indian health in Guatemala. West J Med 1988 Apr; 148:474-476)

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cones rising majestically from the lake: Atitlan, Toliman, and San Pedro.

We sallied forth from Sololá every morning in a four-wheel-drive jeep without which the stony, potholed dirt trails with perilously steep flanking sides would have been unnegotiable. With slope grades of 30% and all cultivation done by hand, one can only marvel at the challenges to ingenuity and endurance met by those who must till, plant, and divert the waters of mountain springs for irrigation in these dizzying heights (Figure 2). From aqueducts men, women, and children spend hours ladling water into small buckets and scattering it among the plants. Everywhere—perhaps the most distressing sight of all—there were the human beasts of burden of all ages laden, like their ancient ancestors, with staggering loads. This fact of life explains their most commonly voiced complaint, backache.

How does one describe the milieu in which we worked, a setting so radically different from that familiar to physicians in this country? What follows is a composite picture of all the villages we serviced. Our team had two physicians and one nurse practitioner who toiled tirelessly. Our priest hosts, admirably dedicated to the spiritual and physical needs of their parishioners, are still faithful to the conventional doctrines of their church concerning contraception. Splendidly humane in their social outlook and keenly aware of the maternal devastation wrought by annual childbirth, they neither promoted nor interfered with the efforts of our nurse colleague. We arrived at our work sites at about 9 AM to find our patients already in front of our assigned office space, often a small, cold, unlit storage room without water or electricity. A not infrequent alternative site was a clearing under the sun. As we set up shop, dozens of stragglers descended from their hillside huts, lengthening the waiting line (Figure 3) even as we later announced the imminent close of our session. Most of our clinical work was done on rough-hewn wood benches, which we used for examining tables and for storing our supplies. Our instruments were basic: a sphygmomanometer, an otoscope, and two stethoscopes (Figure 4). There were no illuminating lamps, gloves, vaginal specula, injectables, scalpels, or sterile bandages. Privacy was unknown; the entire community, our uncritical audience, pushed irresistibly ever closer to the arena of our work. They were privy to our questions, posed in Spanish, and to patient responses in Quiché or Cakchiquel, the two common tribal dialects of this region. The only suggestion of privacy, dictated by our own established habit, was the raising of a blanket to shield a female abdomen from the curious but not prying eyes of neighbors. Add to the confusion of human numbers, inside and outside, a procession of cackling hens and crowing roosters pecking for food underfoot, and the picture, though delightfully pastoral, is hardly tranquil.

Figure 2.—Terraced farms.

Without our interpreters, who were village men of some authority, our work would have been impossible. We began with the simple question, *"Que problema tiene?"* (What is your problem?). The nearly universal reply was, *"Me duele mucho"* (I hurt a lot), from which proceeded the usual pursuit of clues designed to arrive at some tentative diagnosis. Two organ systems dominated the symptomatic scene, the gastrointestinal and musculoskeletal. The remedy we recommended for the latter was not a jacuzzied hot tub at the end of a work day or a few days of rest. Water boiled over the outdoor cooking fire can be useful as a hot compress, perhaps the more so in combination with a simple analgesic, which we dispensed by the thousands in small, coned containers we fashioned from discarded newspapers. If improvement followed, we urged patients to purchase aspirin at the local pharmacy; if there was no relief, we recommended a visit to one of Sololá's hospitals. This suggestion was not made lightly, since the distance to that city by circuitous roads may be 30 to 40 km (19 to 25 miles) or more, a daunting walk for the seriously ill or disabled. Public transportation traverses only the few main highways.

The entire length of the Indian digestive tract, from mouth to anus, may be heir to some dysfunction. Peptic disorders, gas, cramps, pain, and diarrhea, rarely constipation, were the

Figure 3.—The clinic waiting room.

Figure 4.—The doctor's office.

most common complaints. We tried to make educated guesses about etiology that might justify our generous dispensation of the only two appropriate medications in our severely abbreviated formulary: bismuth subsalicylate (Pepto-Bismol) and piperazine phosphate. To these we added some ingenuous dietary advice. Mothers often provided diagnostic assistance for their children's abdominal symptoms, mentioning lumbrices (roundworms), whether seen or not. Somewhat comforted by a ready-made, maternal impression, no doubt based on long experience, we doled out our lone anthelmintic with undisciplined extravagance. When an ascarid was sighted in the stool or vomitus or was observed exiting from a child's nose, our therapeutic joy was boundless.

Frequently seen in our patient population were the upper respiratory infections in children, and occasionally, purulent otitis media, scabies, pediculosis, and impetigo. In adults, few of whom are smokers, bronchitis was noted often. Clinical tuberculosis, hypertension, coronary artery disease, thyroid dysfunction, and malignancies were rarely observed. Endemic malaria does not exist at this altitude, but the episodic chills and fever of Guatemalan paludism were present in two young women who had migrated to the Highlands region from the southern coastal plains, where it abounds. Inguinal hernias, which I had seen with astonishing frequency in African men with similarly rigorous work habits, were virtually absent. The infectious diseases of childhood were not at all in evidence, reflecting their seasonal absence or a modest government program of immunizations by mobile units that encompasses enough children to ensure adequate herd immunity.

Despite the existence of a wide range of crops and of supporting small flocks of poultry and herds of cattle, sheep, and goats, the almost unvarying staples of the Mayan diet are corn and beans. The greens, tomatoes, potatoes, fruit, eggs, poultry, and dried fish seen at all the public street markets are "cash crops," vended primarily to the *mestizos* (mixed European and Indian) and *ladinos* (upwardly mobile Indians). With large groups of patients—mainly women and children—assembled, waiting to be seen at our clinics, we persuaded our community leaders (interpreters) to talk to them about simple nutrition. The approach was a statement without explanation: better health for children and adults demands a diet that must include foodstuffs available at the market but so infrequently eaten. With a centuries-old, culturally determined cuisine and a political system that denies the Indians ownership of land, we had few illusions that a one-minute speech would have any lasting effect.

Our medications were simple and rarely specific. They were all that was available, representing small quantities of samples we had brought with us and much larger amounts sent to this parish by Caritas, one of the international charitable arms of the Catholic Church. In this instance, at least, there seemed to be no effort made to match the generous gift of samples with local patient needs. Skin fresheners, dandruff lotions, and anesthetic toothpastes were in good supply but in nonexistent demand. Oral tetracycline was the sole antibiotic. We had no mebendazole or metronidazole for intestinal parasites, and no gamma-benzene hexachloride for endemic pediculosis and scabies. Our beta-blockers, coronary dilators, and oral antidiabetics found no use. We wrote prescriptions sparingly, heeding the admonitions of our interpreters that both distance from town and lack of cash would discourage their purchase. Without fundamental changes in life-styles, symptomatic improvement or cure would at best be fleeting. For patients urgently in need of antibiotics, our importunings were often melodramatic, if not always successful. For an acutely ill patient we found room in the jeep for transportation to the local hospital. We wrote prescriptions on any scrap of paper. Local pharmacies have few restrictions on their dispensing practices. An over-the-counter request by anyone, for any drug, is honored. Ours, at least, had some reasonable, if undocumented, basis for use.

Family planning is almost unknown in these isolated mountain communities. One of the international family planning agencies had recently opened an office in Sololá. The secretary reported a patient load of three to four persons a week—women and men who live in the city and belong to the emerging, entrepreneurial class. The program represents a beginning, but a long and intensive period of education will be necessary before Indians will be ready to seek help from such a source. Accompanying the informative process there must also be fundamental change in the economics of Indian existence. They have to be convinced that family survival is possible without the uninterrupted production of children. The usual response to the question, "How many pregnancies have you had?" was 10 to 14. The signs of premature aging among women were invariable. At age 35 they are drained of their vitality: haggard, toothless, wrinkled, yet struggling daily to fulfill their obligations to their families.

Sexually transmitted diseases appear to be almost unknown among the Mayans. Not one suggestive case appeared among all the villagers we saw. Astonishing, too, in the face of excessive childbearing, we found little symptomatic evidence of reproductive tract pathology. Lacking pediatric training we were not always comfortable with some of the health problems of nursing infants. What did strike us forcefully was the intimacy of the relationship between mother and child. In her waking hours the mother was never out of close contact with her offspring, whether walking, shopping at the street market, working in the fields, or preparing the family meal. It was not the plaintive cry of an infant that hindered examination of its lungs. More often it was a solicitous mother, cradling her child close to her body, ever ready to assuage its mildest whimper. Her breast, poised to feed a crying, receptive mouth, intervened to separate our stethoscope from the chest wall.

What, if anything, did we accomplish in providing such elementary health services in these isolated mountain villages? Measured in terms of immediate saving of lives, surely very little. We reduced morbidity but only briefly. It is unlikely that we modified life-styles. Perhaps our repeated exhortations to boil water for drinking, to dispose safely of fecal wastes, to expand the diet beyond corn and beans, and to space pregnancies will take root among a few of our patients.

Perhaps the most important legacy of such brief working visits is to convey a sense of caring and to introduce the concept of avoidable illness through basic modifications of the environment. Long before physicians and nurses will choose to settle in these areas, the immediate and pressing need is for an infusion of trained health promoters. These should be villagers, known and trusted by the people, capable of identifying and treating the common diseases and of immunizing children, as well as recognizing what is unmistakably beyond their limited skills.

Family Practitioners' Immunization Consent Practice Washington State, 1986

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Of 400 Washington State family practitioners surveyed in 1986, 46% of those who give routine immunizations reported that they require written parental consent before administering vaccine. In all, 57% of respondents said they discuss diphtheria-tetanus-pertussis, measles-mumps-rubella, and oral polio vaccine with their patients. Nearly half provide written information on these immunizations, except for inactivated polio vaccine, for which fewer than 20% of the physicians surveyed provide verbal or written information.

(Holt VL, Coombs JB, Marcuse EK: Family practitioners' immunization consent practice—Washington state, 1986. West J Med 1988 Apr; 148:477-479)

In 1978, a small minority of Washington State pediatricians reported that they routinely obtained written consent from parents before giving immunizations.[1] No information about immunization consent practices of other practitioner groups is available. Increased publicity about adverse effects of routine childhood immunizations and physician concern about litigation prompted us to examine the current consent practice of family practitioners in our community.

Methods

We mailed a one-page questionnaire (Figure 1) concerning routine childhood immunization practices (discussion with parents, provision of written information, requirements for written or verbal consent for immunization), and respondent-related data (type of practice, decade of graduation, and residency history) to every third practitioner on the mailing list of the Washington State chapter of the American Academy of Family Practice.

Of the 400 physicians queried, 319 responded, for an overall response rate of 80%. A total of 302—95% of the respondents—reported that they administer one or more types of routine immunizations. Our data base consists of their responses. Because all respondents did not answer every question, the number for each question was sometimes lower than the number of respondents in each category. The data were analyzed using the Centers for Disease Control's microcomputer program EpiInfo.

Results

A parent's signature as evidence of having provided information or obtained consent or both was reportedly required by 46% of the family physicians who give immunizations. The percentage of practitioners requiring written consent rose with more recent graduation from medical school, ranging from 25% of those graduating in the 1950s to 61% in the 1980s (Table 1).

Of 181 family practitioners who had completed a three-year residency program (59% of respondents), 57% said they required written consent. Of 120 not completing a residency (41% of respondents), written consent was used by 29%. This difference is statistically significant ($P < .001$, using Yates corrected χ^2 test).

Of the 164 respondents not requiring written consent for immunization, 86 (28% of all family practitioners) did require verbal consent. Written or verbal consent before administering immunizations was never obtained by 14% of the respondents.

In all, 57% of the family practitioners said they routinely discussed diphtheria-tetanus-pertussis (DTP), measles-mumps-rubella (MMR), and oral polio vaccine (OPV), and half of all respondents provided written information. Because there were no meaningful differences in survey responses concerning these three vaccines, they were grouped and analyzed together.

Hemophilus influenzae type B polysaccharide vaccine was administered by 90% of the family practitioners surveyed. Of the respondents, 60% said they discussed this vaccine with patients, and 38% provided written information. Inactivated polio vaccine (IPV) was discussed by 17% of the respondents, while 19% supplied written materials.

The questionnaire asked for the source of written information used, allowing multiple responses. Some type of written information was provided by 69% of the respondents. State and local health departments were cited as an information source by 26% of those providing information, the Centers for Disease Control by 23%, pharmaceutical companies by 20%, Group Health Cooperative of Puget Sound by 15%, and Seattle Children's Hospital and Medical Center by 7%. A

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ABBREVIATIONS USED IN TEXT

DTP = diphtheria-tetanus-pertussis
IPV = inactivated polio vaccine
MMR = measles-mumps-rubella
OPV = oral polio vaccine
HMO = health maintenance organization

total of 12% stated they wrote and distributed their own information. Patients were always provided information on DTP, MMR, and OPV immunizations by 61% of the respondents who had completed a residency, while only 32% of the non-residency-trained respondents always provided this information ($P < .001$).

Discussion

Nearly half of the family practitioners surveyed in Washington State reportedly provide written information on the risks and benefits of immunizations and require written consent for immunization. This probably reflects a recent change in practice since a 1978 study of Washington State pediatricians, in which half of the respondents reported discussing immunizations with parents, 15% gave written information, and only 12% required written consent for immunization.[1]

The current study also may be compared with our parallel 1986 study of 399 Washington State pediatricians and allied health professionals, which found that 62% of the pediatricians and 86% of the allied professionals required written parental consent for immunization.[2] The pediatricians' use of written consent corresponds to that of family practitioners who have completed a family practice residency.

The differences between residency-trained and non-residency-trained family practitioners in immunization consent practice may be reflective of their decade of medical school graduation. Residency-trained family practitioners are more recent graduates, and our parallel study of pediatricians has shown that those graduating medical school in recent decades are more likely to require written consent than earlier graduates, even when almost all are residency-trained.[2] The difference seen may also reflect differences in types of practice, since more health maintenance organization (HMO) physicians are residency-trained than not, and HMOs generally emphasize provision of written information and written immunization consent.

Fewer than 20% of physicians responding stated that they provide verbal or written information on IPV. This response supports our observation that IPV is not readily available or extensively used by private family physicians at this time.

TABLE 1.—*Washington State Family Practitioners' Use of Written Consent by Decade Graduated Medical School*

Decade Graduated	No.	Percent Requiring Written Consent
1940s	7	29
1950s	65	25
1960s	40	30
1970s	152	56
1980s	36	61

Family Practice Immunization Questionnaire

1. Some physicians provide patients and parents with information on the benefits and risks of routine immunizations.

A. How frequently do you *Discuss* the benefits/risks of each of these? (Circle for *each* vaccine)

	Almost Never	Sometimes	Almost Always	Do Not Administer
DTP*	1	2	3	4
MMR†	1	2	3	4
H. flu b‡	1	2	3	4
OPV§	1	2	3	4
IPV‖	1	2	3	4

B. How frequently do you *Provide Written Information* on each of these vaccines? (Circle for *each* vaccine)

	Almost Never	Sometimes	Almost Always
DTP*	1	2	3
MMR†	1	2	3
H. flu b‡	1	2	3
OPV§	1	2	3
IPV‖	1	2	3

C. If you do provide written information, who publishes the material? (Circle one or more)

1. Centers for Disease Control
2. Seattle Children's Hospital and Medical Center
3. Group health
4. Pharmaceutical company
5. Don't know
6. Other (specify)_____

2. Some physicians obtain formal consent for immunization. How frequently do you do any of the following? (Circle for each option A, B, and C)

	Never	Sometimes	Always
A. Obtain a parent/guardian signature as evidence of having provided information or obtained consent	1	2	3
B. (1) Obtain a parent/guardian's *specific verbal consent*	1	2	3
(2) Record verbal consent and/or provision of information in the patient's record	1	2	3
C. Provide immunization as part of routine care without obtaining a specific verbal consent	1	2	3

3. Which category best describes your practice? (Circle one)

1. Private practice
2. University affiliated
3. Group health/other health maintenance organization
4. Government: federal, county, etc.
5. Other (specify): _____

4. Circle the decade you graduated from medical school:

30 40 50
60 70 80

5. Did you complete a full three-year residency training program?

☐ Yes ☐ No

*DTP = diphtheria-tetanus-pertussis
†MMR = measles, mumps, rubella
‡H. flu b = *Hemophilus influenzae* type B polysaccharide
§OPV = oral polio vaccine
‖IPV = inactivated polio vaccine

Figure 1.—Family practice immunization practice questionnaire.

Additional unsolicited comments were appended to some respondents' questionnaires. The most common theme was a medicolegal concern; four respondents stated that they had limited or ceased routine administration of immunizations due to concern about litigation.

It remains to be shown that written consent forms increase the number of well-informed parents or decrease litigation. Use of such forms, however, may facilitate communication between parent and physician and thereby assist physicians in fulfilling their obligation to inform patients of "the benefits and risks of preventive and therapeutic procedures including immunizations" as outlined by the American Academy of Pediatrics.[3]

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1. Marcuse EK: Pediatricians' immunization consent practice, Washington state. Pediatrics 1979; 63:419-422

2. Holt VL, Marcuse EK, Coombs JB: Pediatricians' immunization consent practice, Washington state. Am J Dis Child 1987; 141:734-735

3. American Academy of Pediatrics: Report of the Committee on Infectious Diseases, 20th Ed. Evanston, IL, 1986; p 3

Book Reviews

BRACHIAL PLEXUS INJURIES—Robert D. Leffert, MD, Associate Professor of Orthopaedic Surgery, Harvard Medical School, and Chief of the Surgical Upper Extremity Rehabilitation Unit and of the Department of Rehabilitation Medicine, Massachusetts General Hospital, Boston. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1985. 235 pages, $50.

Brachial Plexus Injuries is an extensive monograph consisting of 11 chapters and 243 total pages covering the subject in detail. It includes chapters on the anatomy of the brachial plexus, closed and open injuries of the brachial plexus, supraclavicular and infraclavicular injuries, assessment of the neuropathy related to the brachial plexus, and gives us detailed plans for both conservative and operative treatment. The final chapter is on peripheral reconstruction of the upper limb following brachial plexus injury.

Brachial plexus injury is one of the major unresolved problems in trauma. Robert D. Leffert, MD, is one of the acknowledged world experts in management of the injury. Thus, his approach to this challenging problem should be of interest to the neurosurgeon, orthopedic surgeon, hand surgeon, and perhaps the general surgeon interested in trauma, as well.

F. WILLIAM BLAISDELL, MD
Professor and Chair
Department of Surgery
University of California
Davis

* * *

REPRODUCTIVE FAILURE—Edited by Alan H. DeCherney, MD, The John Slade Ely Professor of Obstetrics and Gynecology and Director, Division of Reproductive Endocrinology, Yale University School of Medicine, New Haven, Connecticut. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1986. 302 pages, $45.

Dr DeCherney has edited a simple, easy-to-read textbook that presents a complex topic in a straightforward manner. He has combined in one book the scope of reproductive failure. Most texts in this area focus on infertility and leave the problems of ectopic pregnancy, habitual abortion, and so forth, to other authors. By combining these topics in one book, Dr DeCherney has focused on the major issue that our patients face: taking home a viable infant.

The book begins with a fascinating review of the history of reproductive failure. This is followed by a discussion of the epidemiology, which is well written and presents the statistics from a different point of view. I was pleased to see that the authors also included data on the male factor. Although found in reference books on infertility, it is not usually discussed in obstetric or gynecologic books dealing with other problem areas nor is it covered in this much detail in books on infertility. The only concern I have with the book is in the area of infertility surgery. This is a very complex topic, and the author presents it in a clear concise fashion; however, the implication is that it can be done by anyone.

In summary, I would recommend this book to any physician who deals with patients with reproductive failure.

RALPH W. HALE, MD
Department of Gynecology and Obstetrics
University of Hawaii John A. Burns School of Medicine
Honolulu

* * *

SCANNING ELECTRON MICROSCOPY OF NORMAL AND ABNORMAL HUMAN SKIN—Walter H. Wilborn, PhD, Professor of Anatomy and Director; Barbara M. Hyde, MTA, Electron Microscopy Specialist and Research Associate, and Leopoldo F. Montes, MD, Adjunct Professor of Anatomy and Dermatology Research, Electron Microscopy Center, University of South Alabama College of Medicine, Mobile. VCH Publishers, Inc, 220 E 23rd St, Suite 909, New York, NY 10010, 1986. 219 pages, $49.50.

Visually oriented physicians and scientists may desire to know how the microscopic anatomy of the skin translates into a three-dimensional structure. For such individuals, scanning electron microscopy (SEM) provides a means to learn how the pieces fit together.

In *Scanning Electron Microscopy of Normal and Abnormal Skin,* Wilborn, Hyde, and Montes provide a fascinating atlas of the structure of skin. This represents the first comprehensive attempt to contruct an SEM picture of the development of fetal skin, of the structure of normal adult skin, and of the alterations in disease entities. The electron micrographs are well-labeled and provide an opportunity for the non-expert to appreciate the complex three-dimensional anatomy of the skin. The authors, fortunately, anticipated that individuals unfamiliar with SEM might use this atlas, so they provide the reader with a concise, simplified explanation of the technique and the equipment used. They also have included appropriate illustrations of cutaneous anatomy, as well as examples of light microscopic and transmission electron-microscopic findings. Each section of the book also includes a pertinent bibliography.

Not all of the micrographs are of excellent quality, and some repeat examples of the same features shown in adjacent micrographs. Although interesting examples of SEM findings in acne, psoriasis, seborrheic keratosis, capillary hemangioma, basal cell carcinoma, squamous cell carcinoma, keratoacanthoma, and pigmented nevus are shown, for the most part, the scanning electron micrographs included do not significantly enhance our understanding of the pathogenesis of these disease entities.

This book is not one that should be on everyone's shelf. However, it represents the compilation of a series of unique micrographs of the skin and should be a valuable resource in medical libraries. Those scientists with special interest in fetal skin, structure and function of the skin, and electron microscopy may find this atlas of sufficient interest to want personal copies.

The authors of this book should be commended for integrating scanning electron microscopy findings into a unique, understandable volume on the structure of the skin.

J. CLARK HUFF, MD
Associate Professor of Dermatology and Medicine
University of Colorado Health Sciences Center
Denver

* * *

WOUND CARE—William M. Cocke, Jr, MD, Professor of Surgery; Raleigh R. White IV, MD, Professor of Surgery; Dennis J. Lynch, MD, Professor of Surgery and Chief, and Charles N. Verheyden, MD, PhD, Associate Professor of Surgery, Division of Plastic Surgery, Department of Surgery, Scott and White Clinic, Texas A&M University College of Medicine, Temple, Texas. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1986. 113 pages, $25.

Wound Care summarizes the basic principles of wound healing and illustrates some of the fundamental concepts of wound management with selected cases representating common acute, subacute, and chronic wounds. The indications for simple primary wound closure are contrasted with open wound care and delayed closure. Specific examples emphasize the role of debridement and dressing care in wound control as prerequisites for either spontaneous healing or secondary closure. Systemic and local factors that inhibit wound healing are identified, together with recommended correction of reversible factors such as malnutrition, infection, hypoxia, and hyperglycemia. The techniques suggested for wound repair range from simple suture, skin grafting, and local flap transposition to distant free tissue transplantation. Separate consideration is given to the management of specific wounds such as venous stasis ulceration, burn injury, bites, and the "difficult" wound that is complicated by radiation injury, malignancy, osteomyelitis, and threatened limb loss.

This monograph is a useful introduction to the broad and complex subject of wound healing. Basic definitions of wound healing physiology, wound pathology, and surgical principles are accurately and simply stated but perhaps necessarily incomplete as a result of the brevity of the volume. Notable was the absence of reference to wound bacteriology in the discussion of wound control, when the use of quantitative cultures and systemic or topical antimicrobial agents in both open and burn wounds has been shown to substantially influence both the accurate timing and the success of delayed wound closure. Similarly, a brief discussion of the techniques of local anesthesia administration and the pharmacology of lidocaine (with and without epinephrine) and its toxicity would have complemented the discussion of acute suture repair of simple and complex lacerations.

Although principles of wound care are illustrated by clinical case examples, many of the management solutions cannot be interpreted as a practice guide for the nonsurgeon. For example, the decisions to debride an ischemic amputation stump, to allow a facial wound to heal by secondary intention, or to remove a breast implant clearly should be made and executed by the primary surgeon. Many of the more challenging wounds involving exposure of bone, major vessels, and tendons require consultation with plastic surgeons or at least reconstructive surgeons with expertise in wound coverage and familiarity with techniques such as skin grafting, flap design, and microvascular tissue transfer. A similar approach of consultation is standard practice for the repair of complex facial soft tissue injury, and such wounds are not appropriately triaged to health care personnel without specialty training.

In summary, *Wound Care* is a useful introductory volume for health care professionals in primary care, for medical students, and possibly for nonsurgeon physicians. Its scope is broad as a brief, updated overview of the fundamental generic approaches to wound care, but its depth is not sufficient either as a practical guide for nonsurgeon physicians or as a practice guide for the nonspecialized surgeon.

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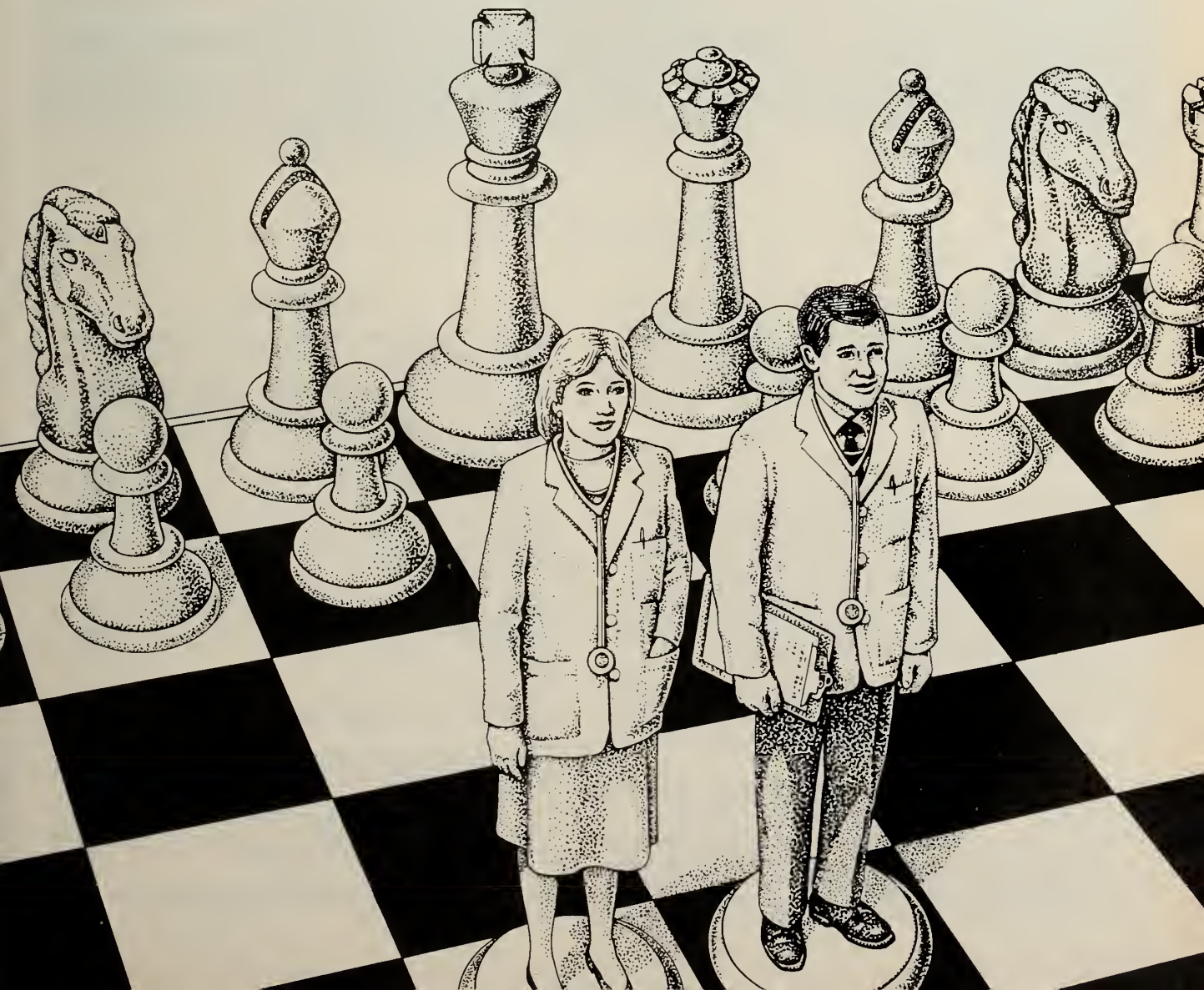

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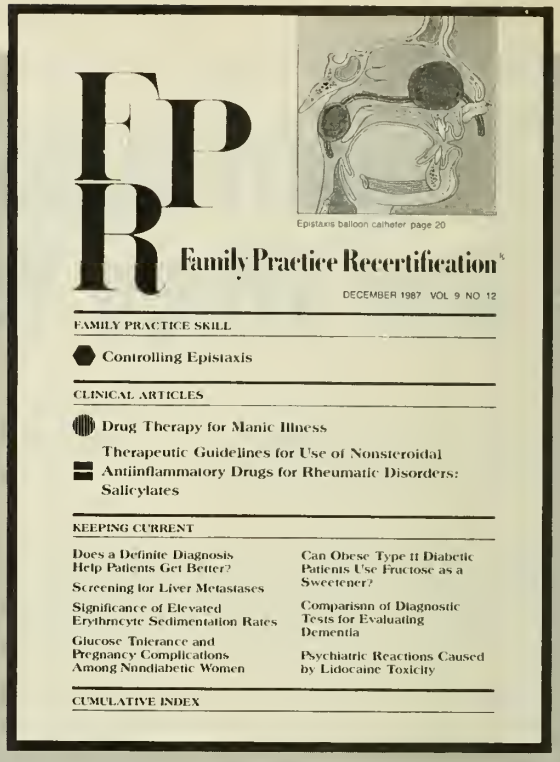
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CONTINUING MEDICAL EDUCATION

(Continued from Page 418)

June 20-24—**Advances in Internal Medicine.** UCSF at San Francisco. Mon-Fri. 32 hrs. $485. Contact: UCSF.

September 22-24—**International Symposium on Medical Virology.** UCI at Ramada Renaissance Hotel, San Francisco. Thurs-Sat. Contact: Dr Luis M. de la Maza, Department of Pathology, Rt 84, UCI Medical Center, 101 City Drive S., Orange, 92668. (714) 634-6868.

OB/GYN

April 21-23—**10th Annual Orange County OB/GYN Congress.** Orange County Obstetrical and Gynecological Society at Westin Hotel, South Coast Plaza, Costa Mesa. Thur-Sat. 15 hrs. $300. Contact: Paula Rogers, PO Box 1297, Orange 92668. (714) 978-1260.

June 30-July 3—**6th Annual Controversies in Obstetrics & Gynecology.** Center for Health Education at Mauna Kea Beach Hotel, Hawaii. Thur-Sun. Contact: The Center for Health Education, 2081 Atlantic Ave., PO Box 1428, Long Beach, 90801-1428. (213) 595-3811.

August 19-21—**1988—Office Gynecology for the Primary Care Physician.** Continuing Medical Education Associates and San Diego State University at Hyatt Islandia, San Diego. Fri-Sun. 18 hrs. $295. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

November 10-13—**Current Issues in Perinatal Medicine.** UCI at Marriott's Rancho Las Palmas Resort, Palm Springs. Thurs-Sat. Contact: UCI.

November 13-19—**11th Annual Review Course in Clinical Obstetrics & Gynecology.** The Center for Health Education at Westin South Coast Plaza Hotel, Costa Mesa. Sun-Sat. Contact: The Center for Health Education, 2081 Atlantic Ave., PO Box 1428, Long Beach, 90801-1428. (213) 595-3811.

PEDIATRICS

April 29-30—**21st Annual Advances and Controversies in Clinical Pediatrics.** UCSF at Mark Hopkins Hotel, San Francisco. Fri-Sat. 16.5 hrs. Contact: UCSF.

June 24-25—**Current Concepts in Child Neurology 1988.** Children's Hospital San Diego at the Holiday Inn Montgomery Field, San Diego. Fri-Sat. 10 hrs. Contact: Continuing Medical Education Office, Children's Hospital. (619) 576-4072.

August 22-24—**Pediatrics Update: 1988.** San Diego State University at Hyatt Islandia, San Diego. Mon-Wed. 18 hrs. $295. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

October 15-20—**American Academy of Pediatrics Annual Session.** AAP. Sat-Thurs. Contact: AAP, 1801 Hinman Ave., Evanston, IL 60201.

October 22-29—**13th Annual Pediatrics for the Practitioner: A Pediatric Symposium.** Center for Health Education at Mauna Kea Beach Hotel, Hawaii. One week. Contact: The Center for Health Education, PO Box 1428, Long Beach 90801-1428.

PSYCHIATRY

April 15-16—**3rd Annual Work and Mental Health Symposium.** UCSF at Holiday Inn Union Square, San Francisco. Fri-Sat. 12 hrs. $200. Contact: UCSF.

April 23-24—**The Cutting Edge 1988: Innovations in Psychotherapy: Helping Individuals and Couples to Change.** UCSD at Hotel Del Coronado, San Diego. Sat-Sun. 13 hrs. $275. Contact: UCSD.

May 23-24—**Child Abuse.** UCD at Holiday Inn Holidome, Sacramento. Mon-Tue. Contact: UCD.

(Continued on Page 483)

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American Board of Anesthesiology, American College of Anesthesiology, Chief of Anesthesiology — Emanuel Medical Center, Member of American Academy of Pain Medicine

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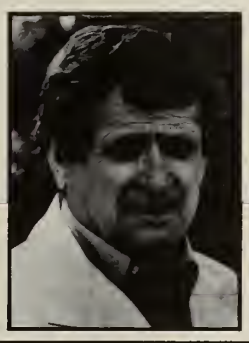

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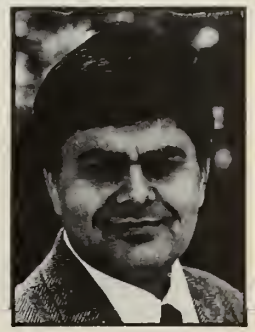

CONTINUING MEDICAL EDUCATION

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RADIOLOGY

April 29-May 1—**13th Annual Spring Diagnostic Ultrasound Conference.** Los Angeles Radiological Society at Century Plaza Hotel, Los Angeles. Fri-Sun. 20 hrs. $325. Contact: Christopher M. Rose, MD, c/o Los Angeles Radiological Society—SDUC, PO Box 91215, Los Angeles 90009-1215. (213) 642-0921.

May 3-7—**8th Annual Post Conference Seminar.** Los Angeles Radiology Society at Kahala Hilton Hotel, Honolulu. Tues-Sat. 19 hrs. $395. Contact: Christopher Rose, MD, c/o Los Angeles Radiological Society—SDUC, PO Box 91215, Los Angeles 90009-1215. (213) 642-0921.

July 28-31—**Second Annual Symposium on Magnetic Resonance Imaging.** Hoag Memorial Hospital at Ritz-Carleton Hotel, Laguna Niguel. Thurs-Sun. $395. Contact: Mary J. Ryals and Associates, PO Box 920113, Norcross, GA 30092-0113. (404) 641-9773.

August 1-5—**Modern Radiology Practice.** UCSD at Fess Parker Red Lion Resort, Santa Barbara. Mon-Fri. 30 hrs. $425. Contact: Mary J. Ryals and Associates, PO Box 920113, Norcross, GA 30092-0113. (404) 641-9773.

August 25-28—**Fourth Annual Physics and Biology of Radiology.** UCSD at La Jolla Village Inn. Thurs-Sat. 25 hrs. $395. Contact: Mary J. Ryals and Associates, PO Box 920113, Norcross, GA 30092-0113. (404) 641-9773.

September 9-11—**Fourth Annual Sonography Update and Review Course.** UCSD at Hanalei Hotel, San Diego. Fri-Sun. 17 hrs. $375. Contact: Mary J. Ryals and Associates, PO Box 920113, Norcross, GA 30092-0113. (404) 641-9773.

SURGERY

April 14-16—**Postgraduate Course in General Surgery.** UCSF. Thur-Sat. Contact: UCSF.

April 15-17—**The 5th Annual San Diego Meeting on Arthroscopic Surgery of the Shoulder.** Tri-City Orthopaedic & Sports Physical Therapy Medical Group, Inc. at La Jolla Marriott Hotel, La Jolla. Fri-Sun. Contact: James C. Esch, MD, 3905 Waring Rd, Oceanside 92056. (619) 724-9000.

April 16-23—**Management of the Surgical Patient.** Stanford University Medical Center at The Westin Mauna Kea, Hawaii. Sun-Fri. 25 hrs. $495. Contact: Stanford.

April 29—**Ultrasonic Liver Surgery: A Hands-on Workshop.** UCD at Hyatt Regency, Sacramento. Fri. 8 hrs. $250. Contact: UCD.

June 20-24—**First International Symposium on Orbital Plastic Surgery.** Plastic Surgery Education Foundation at San Francisco. Mon-Fri. Contact: PSEF, 233 N. Michigan Ave, Suite 1900, Chicago, Illinois 60601.

August 18-21—**Discussions of Current Hand Care Concepts.** Plastic Surgery Education Foundation at San Diego. Thurs-Sun. Contact: PSEF, 233 N. Michigan Ave, Suite 1900, Chicago, Illinois 60601.

September 17—**Summary of Clinical Use of Argon, YAG and CO2 Lasers for Cutaneous Lesions.** Palo Alto Medical Foundation at Palo Alto Medical Clinic. Sat. 6 hrs. Contact: Palo Alto Medical Clinic, 300 Homer Ave, Palo Alto 94301. (415) 321-4121.

OF INTEREST TO ALL PHYSICIANS

April 15-17—**Office Orthopedics for the Primary Care Physicians.** CMEA & Sharp Memorial Hospital at San Diego Princess Hotel. Fri-Sun. 20 hrs. $395. Contact: Jacqueline Shiller, P.O. Box 84296, San Diego, 92138. (619) 223-2997.

April 16-23—**Current Concepts in Allergy and Clinical Immunology.** University of Washington at Maui, Hawaii. One week. Contact: U/W School of Medicine, Div of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

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CONTINUING MEDICAL EDUCATION

(Continued from Page 483)

April 22-23—**Comprehensive Care of the AIDS Patient: A Workshop.** UCSF at San Francisco. Fri-Sat. Contact: UCSF.

April 23—**Current Concepts in Liver Diseases.** Scripps Clinic and Research Foundation at Amphitheater, Scripps Clinic, La Jolla. Thur. 6 hrs. $125. Contact: Bonny Mower, 10666 N. Torrey Pines Road, La Jolla, 92037. (619) 457-8556.

May 5—**Public Lecture Series on Aging.** UCLA at the Westwood Methodist Church, Los Angeles. Thurs. $10. Contact: UCLA.

May 6-8—**Diagnosis and Management of Respiratory Diseases.** Medical Education Resources at Caesars Palace, Las Vegas, Nevada. Fri-Sun. 11-13 hrs. $225-$295. Contact: MER, 5080 S. Rapp St., Suite 202, Littleton, CO 80120. (800) 421-3756.

May 11—**Diabetes Mellitus.** Loma Linda University at the Lobby Level Amphitheater. Wed. $65. Contact: LLU.

May 12-15—**Decentralized Care of People With AIDS: An Educational Seminar for Developmental Approach.** Sonoma County Academic Foundation for Excellence at Flamingo Hotel, Santa Rosa. Thurs-Sun. $275. Contact: Mary Ellen Buechter, SCAFE, 3325 Chanate Rd, Santa Rosa, 95404. (707) 527-4121.

May 14—**4th Annual Physicians Conference.** UCLA at Los Angeles. Wed. 7 hrs. $75. Contact: UCLA.

May 14—**Prevention of Sexually Transmitted Diseases in Teens.** Children's Hospital at the Merritt Peralta Health Education Center, Oakland. Sat. 6 hrs. $60. Contact: Kim Leadon, Children's Hospital, 747 52nd St., Oakland. (415) 428-3021.

May 15-20—**Primary Care Medicine: Update '88.** UCSF at the Waiohai Hotel, Hawaii. Sun-Fri. 20 hrs. $425. Contact: UCSF.

May 26-27—**Current Concepts of Anatomic Pathology.** UCSF. Thur-Fri. Contact: UCSF.

May 31-June 4—**Family Practice Refresher Course.** UCLA at the Miramar-Sheraton Hotel, Santa Monica. Tues-Sat. 36 hrs. $395. Contact: UCLA.

June 2—**Public Lecture Series on Aging.** UCLA at the Westwood Methodist Church, Los Angeles. Thurs. $10. Contact: UCLA.

June 6-10—**Occupational Respiratory Protection.** USC. 4 hrs. Contact: Institute of Safety and Systems Management, 3500 S. Figueroa St., Ste. 202, Los Angeles, 90007. (213) 743-6523.

June 8—**AIDS.** Loma Linda University. Wed. $65. Contact: LLU.

June 11-12—**Procedure Skills for Primary Care Physicians.** Current Concept Seminars at Ibus Hotel, Milbrae. Sat-Sun. Contact: Donald Berman, MD, Current Concept Seminars, 3301 Johnson St, Hollywood, Florida 33021. (305) 966-1009.

June 13-14—**Ergonomics: Building Efficiency and Safety in the Workplace.** USC. Mon-Tues. 2 hrs. Contact: Institute of Safety and Systems Management, 3500 S. Figueroa St., Ste. 202, Los Angeles, 90007. (213) 743-6523.

June 13-17—**Family Practice Refresher Course.** UCI at Sheraton Newport, Newport Beach. Mon-Fri. 44.5 hrs. $575. Contact: UCI.

June 13-18—**UCI Family Practice Refresher Course.** UCI and Memorial Medical Center at Sheraton Newport Hotel, Newport Beach. Mon-Sat. Contact: Memorial Medical Center, PO Box 1428, Long Beach 90801-1428. (213) 595-3811.

June 14-17—**Society of Nuclear Medicine Annual Meeting.** SNM at Moscone Convention Center, San Francisco. Contact: SNM, 475 Park Ave. S., New York, 10016. (212) 889-0717.

June 15-16—**AIDS/ARC: Update 1988.** UCSF at the Civic Auditorium, San Francisco. Fri-Sat. Contact: UCSF.

June 18-19—**Skills Workshop: Flexible Sigmoidoscopy and Colposcopy.** UCI at Sheraton Newport, Newport Beach. Sat-Sun. 16 hrs. $140-ea., $250-both. Contact: UCI.

June 25-26—**10th Annual Poison Control Center Symposium on Toxicology and Poisoning.** UCSF and Continuing Medical Education in Pharmacy at San Francisco. Sat-Sun. 14 hrs. $235. Contact: Continuing Education S/P, UCSF, Box 0446, San Francisco 94143. (415) 476-4194.

July 14-17—**Decentralized Care of People With AIDS: An Educational Seminar for Developmental Approach.** Sonoma County Academic Foundation for Excellence at Flamingo Hotel, Santa Rosa. Thurs-Sun. $275. Contact: Mary Ellen Buechter, SCAFE, 3325 Chanate Rd, Santa Rosa, 95404. (707) 527-4121.

July 15-18—**Caring for People With AIDS and Their Loved Ones.** Concern for Dying: an Educational Council, at Bishop's Ranch, Healdsburg. Fri-Mon. Contact: Penny Weingarten, 250 West 57th St., Room 831, New York, NY 10107. (800) 248-2122.

July 27-31—**Wilderness Medicine '88.** Wilderness Medical Society at Squaw Valley, Lake Tahoe. Wed-Sun. 22 hrs. Contact: Jackie Silva, Coordinator, Mountain Medical Seminars, PO Box 321, Yreka, 96097. (916) 842-4667.

August 3-6—**15th Annual Meeting: The Peruvian American Medical Society** at Westin Bonaventure Hotel, Los Angeles. Wed-Sat. Contact: Hugo Ortiz, MD, Chairman, Scientific Program, 6488 Tamerlane Dr, West Bloomfield, MI 48322.

August 13-20—**8th Annual Symposium on Fine Needle Aspiration.** UCSF at Kaanapali Beach, Maui. 1 week. 25 hrs. Contact: UCSF.

September 15-18—**Decentralized Care of People With AIDS: An Educational Seminar for Developmental Approach.** Sonoma County Academic Foundation for Excellence at Flamingo Hotel, Santa Rosa. Thurs-Sun. $275. Contact: Mary Ellen Buechter, SCAFE, 3325 Chanate Rd, Santa Rosa, 95404. (707) 527-4121.

September 28-30—**Primary Care Medicine: Principles and Practice.** UCSF at the Portman Hotel, San Francisco. Wed-Fri. $365. Contact: UCSF.

November 10-13—**Sexual Literacy: What is it? What do we know? What do we need to know? Whose responsibility is it?** The Society for the Scientific Study of Sex at the Cathedral Hill Hotel, San Francisco. Thurs-Sun. Contact: Bernard Goldstein, San Francisco State University, Biology Dept., 1600 Holloway Ave., San Francisco, 94132. (415) 338-1548.

IDAHO

May 12—**Managing Major Radiation Accidents.** Idaho Falls Medical Society and Idaho National Engineering Laboratory Occupational Medical Program. Thurs. A one-day seminar with optional one-day tour of INEL on May 11. 7 hrs Cat I, ACEP and AAFP Prescribed. $50. Contact: Tom Schumann, MD, PO Box 1625, Idaho Falls 83402-3125. (208) 526-1596.

July 21-23—**Idaho Medical Association Annual Meeting.** Sun Valley. Thurs-Sat. Contact: IMA, 305 W. Jefferson, PO Box 2668, Boise 83701. (208) 344-7888.

MONTANA

September 29-October 1—**Montana Medical Association Annual Meeting.** Heritage Inn, Great Falls. Fri-Sat. Contact: MMA, 2012 11th Ave., Suite 12, Helena 59601. (406) 443-4000.

NEW MEXICO

Information, requests for accreditation and items to be listed should be sent to the chairman of the CME Committee, New Mexico Medical Society, 303 San Mateo NE, Suite 204, Albuquerque, NM 87108 at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 266-7868.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

April 21-23—**10th Annual Pediatric Cardio-Pulmonary Update.** Sheraton Old Town, Albuquerque. Contact: UNM SOM, Office of CME, (505) 277-3942.

(Continued on Page 485)

CONTINUING MEDICAL EDUCATION

(Continued from Page 484)

April 29-May 1—**Southwest Allergy Forum.** Eldorado Hotel, Sante Fe. Contact: UNM SOM, Office of CME, (505) 277-3942.

May 5-7—**NM Medical Society Annual Meeting—AIDS—Reducing the Risk** and **Chemical Dependency Seminar.** Physicians Mutual Liability Insurance Co **Loss Control Seminar.** Albuquerque Hilton Inn. Contact: New Mexico Medical Society, 303 San Mateo NE, Albuquerque 87108. (505) 266-7868.

May 13—**The Physician in Crisis.** Presbyterian Hospital Quality of Life Committee. Contact: Mary Boning, RN, PO Box 26666, Albuquerque 87125. (505) 841-1225.

May 14—**Cardiac Physical Diagnosis Symposium.** Contact: UNM SOM, Office of CME, (505) 277-3942.

May 19-20—**Mental Health Services With Hispanic and Native American Children and Families.** Contact: UNM SOM, Office of CME, (505) 277-3942.

June 2-3—**8th Annual UNM/ACEP Emergency Medicine Symposium.** AMFAC Hotel, Albuquerque. Contact: UNM SOM, Office of CME, (505) 277-3942.

July 18-21—**Ruidoso Family Practice Seminar.** Inn of the Mountain Gods, Mescalero. Contact: NM Chapter, AAFP, PO Box 23070, Albuquerque 87192. (505) 298-5300.

July 22-24—**Diagnosis and Management of Arrhythmia.** Contact: Presbyterian Heart Institute, Albuquerque, (505) 841-1065/(505) 242-2796.

October 28-29—**New Mexico Medical Society Interim Meeting** and **Loss Control Seminar,** Physicians Mutual Liability Insurance Co. Journal Center Pyramid Holiday Inn, Albuquerque. Contact: New Mexico Medical Society, 303 San Mateo NE, Albuquerque 87108. (505) 266-7868.

UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the CME office of the Utah Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. They also must meet the definition of Utah Approved CME Credit for the purpose of medical license reregistration in Utah. Accredited institutions wishing to list AMA Category 1/Utah Approved CME courses here should send information at least two months in advance to the Office of Continuing Medical Education, 540 East Fifth South, Salt Lake City, Utah 84102; or phone (801) 355-5290. For information on CME accreditation or on the CME requirements of the Utah Physicians' Licensing Board, please write the CME office at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution or the CME office for current details.

MEDICAL GRAND ROUNDS

Each Wed—8:00-9:00 a.m. Alternating between University of Utah Medical Center and VA Medical Center, Salt Lake City. Contact: William D. Odell, MD, PhD, Professor and Chairman, Dept of Internal Medicine, Univ of Utah, (801) 581-7606.

* * *

April 22—**Hypercholesterolemia** (Sponsor: UUMC). Fri. Park Hotel, Salt Lake City. Contact: Rosalie Lammle, (801) 581-8664.

May 5-6—**Ethics and Health: Quality Care in the Age of Cost-consciousness** (Sponsor: UUMC). Thurs-Fri. Union Building, University of Utah. Contact: (801) 581-5705.

July 17-22—**6th Annual Update in Clinical Microbiology and Immunology** (Sponsor: UUMC). Sun-Fri. 25 hours. Jackson Hole, Wyoming. Contact: (801) 581-7408.

August 13-15—**Retrieved Implants and Biomaterials** (Sponsor: UUMC). Fri-Sun. Contact: Rosalie Lammle, (801) 581-8664.

(Continued on Page 486)

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1. For therapeutic use in patients with hypokalemia with or without metabolic alkalosis, in digitalis intoxication and in patients with hypokalemic familial periodic paralysis.

2. For the prevention of potassium depletion when the dietary intake is inadequate in the following conditions: Patients receiving digitalis and diuretics for congestive heart failure, hepatic cirrhosis with ascites, states of aldosterone excess with normal renal function, potassium-losing nephropathy, and with certain diarrheal states.

3. The use of potassium salts in patients receiving diuretics for uncomplicated essential hypertension is often unnecessary when such patients have a normal dietary pattern. Serum potassium should be checked periodically, however, and if hypokalemia occurs, dietary supplementation with potassium-containing foods may be adequate to control milder cases. In more severe cases supplementation with potassium salts may be indicated.

CONTRAINDICATIONS: Potassium supplements are contraindicated in patients with hyperkalemia since a further increase in serum potassium concentration in such patients can produce cardiac arrest. Hyperkalemia may complicate any of the following conditions: Chronic renal failure, systemic acidosis such as diabetic acidosis, acute dehydration, extensive tissue breakdown as in severe burns, adrenal insufficiency, or the administration of a potassium-sparing diuretic (e.g., spironolactone, triamterene).

Wax-matrix potassium chloride preparations have produced esophageal ulceration in certain cardiac patients with esophageal compression due to enlarged left atrium.

All solid dosage forms of potassium chloride supplements are contraindicated in any patient in whom there is cause for arrest or delay in tablet passage through the gastrointestinal tract. In these instances, potassium supplementation should be with a liquid preparation.

WARNINGS: Hyperkalemia—In patients with impaired mechanisms for excreting potassium, the administration of potassium salts can produce hyperkalemia and cardiac arrest. This occurs most commonly in patients given potassium by the intravenous route but may also occur in patients given potassium orally. Potentially fatal hyperkalemia can develop rapidly and be asymptomatic. The use of potassium salts in patients with chronic renal disease, or any other condition which impairs potassium excretion, requires particularly careful monitoring of the serum potassium concentration and appropriate dosage adjustment.

Interaction with Potassium Sparing Diuretics—Hypokalemia should not be treated by the concomitant administration of potassium salts and a potassium-sparing diuretic (e.g., spironolactone or triamterene) since the simultaneous administration of these agents can produce severe hyperkalemia.

Gastrointestinal Lesions—Potassium chloride tablets have produced stenotic and/or ulcerative lesions of the small bowel and deaths. These lesions are caused by a high localized concentration of potassium ion in the region of a rapidly dissolving tablet, which injures the bowel wall and thereby produces obstruction, hemorrhage or perforation.

K-DUR tablets contain micro-crystalloids which disperse upon disintegration of the tablet. These micro-crystalloids are formulated to provide a controlled release of potassium chloride. The dispersibility of the micro-crystalloids and the controlled release of ions from them are intended to minimize the possibility of a high local concentration near the gastrointestinal mucosa and the ability of the KCl to cause stenosis or ulceration. Other means of accomplishing this (e.g., incorporation of potassium chloride into a wax matrix) have reduced the frequency of such lesions to less than one per 100,000 patient years (compared to 40-50 per 100,000 patient years with enteric-coated potassium chloride) but have not eliminated them. The frequency of GI lesions with K-DUR tablets is, at present, unknown. K-DUR tablets should be discontinued immediately and the possibility of bowel obstruction or perforation considered if severe vomiting, abdominal pain, distention, or gastrointestinal bleeding occurs.

Metabolic Acidosis—Hypokalemia in patients with metabolic acidosis should be treated with an alkalinizing potassium salt such as potassium bicarbonate, potassium citrate, potassium acetate, or potassium gluconate.

PRECAUTIONS: The diagnosis of potassium depletion is ordinarily made by demonstrating hypokalemia in a patient with a clinical history suggesting some cause for potassium depletion. In interpreting the serum potassium level, the physician should bear in mind that acute alkalosis per se can produce hypokalemia in the absence of a deficit in total body potassium while acute acidosis per se can increase the serum potassium concentration into the normal range even in the presence of a reduced total body potassium. The treatment of potassium depletion, particularly in the presence of cardiac disease, renal disease, or acidosis requires careful attention to acid-base balance and appropriate monitoring of serum electrolytes, the electrocardiogram, and the clinical status of the patient.

Laboratory Tests: Regular serum potassium determinations are recommended. In addition, during the treatment of potassium depletion, careful attention should be paid to acid-base balance, other serum electrolyte levels, the electrocardiogram, and the clinical status of the patient, particularly in the presence of cardiac disease, renal disease, or acidosis.

Drug Interactions: Potassium-sparing diuretics; see **WARNINGS**.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term carcinogenicity studies in animals have not been performed.

Pregnancy Category C: Animal reproduction studies have not been conducted with K-DUR. It is also not known whether K-DUR can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. K-DUR should be given to a pregnant woman only if clearly needed.

Nursing Mothers: The normal potassium ion content of human milk is about 13 mEq per liter. Since oral potassium becomes part of the body potassium pool, so long as body potassium is not excessive, the contribution of potassium chloride supplementation should have little or no effect on the level in human milk.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: One of the most severe adverse effects is hyperkalemia (see **CONTRAINDICATIONS, WARNINGS,** and **OVERDOSAGE**). There have also been reports of upper and lower gastrointestinal conditions including obstruction, bleeding, ulceration, and perforation (see **CONTRAINDICATIONS** and **WARNINGS**); other factors known to be associated with such conditions were present in many of these patients.

The most common adverse reactions to oral potassium salts are nausea, vomiting, abdominal discomfort, and diarrhea. These symptoms are due to irritation of the gastrointestinal tract and are best managed by taking the dose with meals or reducing the dose.

Skin rash has been reported rarely.

OVERDOSAGE: The administration of oral potassium salts to persons with normal excretory mechanisms for potassium rarely causes serious hyperkalemia. However, if excretory mechanisms are impaired or if potassium is administered too rapidly intravenously, potentially fatal hyperkalemia can result (see **CONTRAINDICATIONS** and **WARNINGS**). It is important to recognize that hyperkalemia is usually asymptomatic and may be manifested only by an increased serum potassium concentration and characteristic electrocardiographic changes (peaking of T-waves, loss of P-waves, depression of S-T segment, and prolongation of the QT-interval). Late manifestations include muscle-paralysis and cardiovascular collapse from cardiac arrest.

Treatment measures for hyperkalemia include the following:

1. Elimination of foods and medications containing potassium and of potassium-sparing diuretics.
2. Intravenous administration of 300 to 500 ml/hr of 10% dextrose solution containing 10-20 units of insulin per 1,000 ml.
3. Correction of acidosis, if present, with intravenous sodium bicarbonate.
4. Use of exchange resins, hemodialysis, or peritoneal dialysis.

In treating hyperkalemia, it should be recalled that in patients who have been stabilized on digitalis, too rapid a lowering of the serum potassium concentration can produce digitalis toxicity.

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(Continued from Page 485)

SPONSORS OF COURSES—ABBREVIATIONS

AHA: American Heart Association, Utah Affiliate, 645 E 400 South, Salt Lake City 84102. (801) 322-5601.

BYUHS: Brigham Young University Health Services, McDonald Student Health Center, Brigham Young University, Provo 84602. (801) 378-2771.

CH: Castleview Hospital (formerly Carbon Hospital), RFD 2, Box 46, Price 84501. (801) 637-4800.

CWH: Cottonwood Hospital, 5770 S 300 East, Salt Lake City 84101. (801) 262-3461.

DMC: Dixie Medical Center, 544 S 400 East, St George 84770. (801) 673-9681.

HCH: Holy Cross Hospital, 1045 E First South, Salt Lake City 84102. (801) 350-4744.

ITS: Intermountain Thoracic Society, 1616 S 11th East, Salt Lake City 84105. (801) 484-4456.

LDSH: LDS Hospital, 8th Ave and "C" St, Salt Lake City 84143. (801) 321-1100.

LRH: Logan Regional Hospital, 1400 N 5th East, Logan 84321. (801) 752-2050.

MDH: McKay-Dee Hospital Center, 3939 Harrison Blvd, Ogden 84409. (801) 399-4141.

MVH: Mountain View Hospital, 1000 E Highway 6, Payson 84651. (801) 465-9201.

144: 144th Evacuation Hospital, PO Box 8000, Salt Lake City 84108. (801) 524-3924.

OSS: Ogden Surgical Society, PO Box 9311, Ogden 84409.

PCMC: Primary Children's Medical Center, 320 12th Ave, Salt Lake City 84103. (801) 363-1221.

PVH: Pioneer Valley Hospital, 3460 S 4155 West, West Valley City 84120. (801) 968-9061.

SMH: St Mark's Hospital, 1200 E 3900 South, Salt Lake City 84117. (801) 268-7111.

UOS: Utah Ophthalmological Society, 540 E 500 South, Salt Lake City 84102. (801) 355-7477.

USH: Utah State Hospital, PO Box 270, Provo 84603-0270. (801) 373-4400.

UUMC: University of Utah Medical Center, 50 N Medical Dr, Salt Lake City 84132. (801) 581-2258.

UVRMC: Utah Valley Regional Medical Center, 1034 N Fifth West, Provo 84604. (801) 373-7850.

VAMC: Veterans Administration Medical Center, 500 Foothill Dr, Salt Lake City 84148. (801) 582-1565.

VVMC: Valley View Medical Center, 595 S 75 East, Cedar City 84720. (801) 586-6587.

WASHINGTON

This listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. To list Category 1 programs here please send information at least two months in advance to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 900, Seattle, WA 98121; or phone (206) 441-WSMA.

Brochures and registration forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

April 16-20—**American Radium Society—Seventieth Annual Meeting.** Seattle. Sat-Wed. Contact: Ms Suzanne Bohn, ARS, Philadelphia, PA. (215) 574-3179.

April 18-28—**Review of Physical Medicine and Rehabilitation.** Seattle. Sat-Sat-Tues. Contact: U/W, Maria Lilja, (206) 543-1050.

COURSE SPONSORS AND CONTACT INFORMATION

CME HARBORVIEW—Contact: Gayle Splater, Cytology Continuing Education, Dept. of Pathology, Harborview Medical Center, 325 Ninth Avenue, Seattle, WA 98104. (206) 223-5953.

CME PIERCE COUNTY—Contact: Mrs Maxine Bailey, Executive Director, College of Medical Education, 705 South Ninth, No. 203, Tacoma, WA 98405. (206) 627-7137.

U/W (UNIVERSITY OF WASHINGTON)—Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

WSMA—Washington State Medical Association, Continuing Medical Education, 2033 Sixth Ave, Suite 900, Seattle, WA 98121. (206) 441-9762.

VMMC (VIRGINIA MASON MEDICAL CENTER)—Contact: Linda Orgel, Division of Continuing Medical Education, Virginia Mason Medical Center, PO Box 900, Seattle, WA 98111. (206) 223-6898.

(Continued on Page 488)

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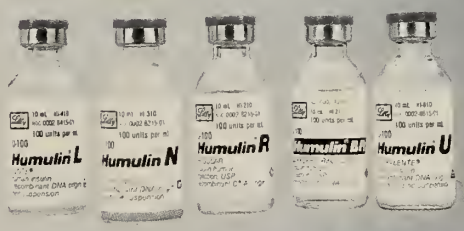

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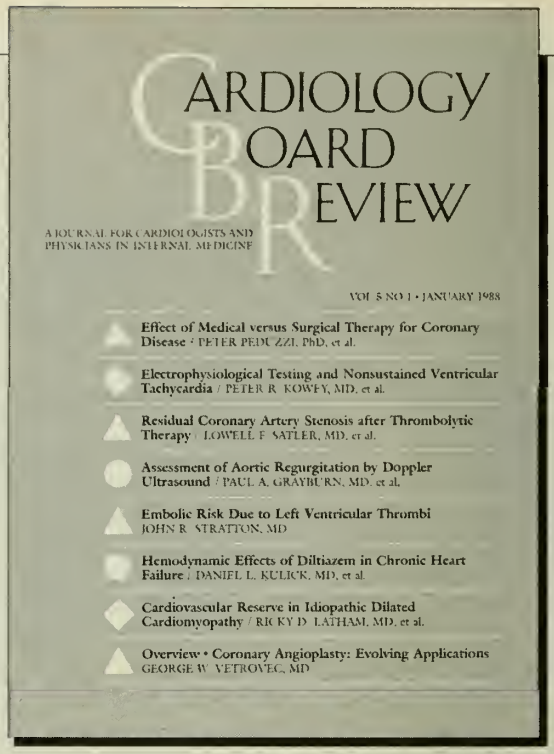


*Journals reviewed include: *Circulation, American Heart Journal, Journal of the American College of Cardiology, British Heart Journal, Chest, The American Journal of Cardiology, The New England Journal of Medicine, Annals of Internal Medicine, American Journal of Medicine*, and *The Journal of the American Medical Association*.

CONTINUING MEDICAL EDUCATION

(Continued from Page 486)

April 19—**Washington State Academy of Ophthalmology Monthly Meeting.** TBA. Tues. Contact: Pattie Smith, (206) 441-9762.

April 20-22—**Death Investigation.** Seattle. Wed-Fri. Contact: U/W, Maria Lilja, (206) 543-1050.

April 28-29—**General Oncology Update for Physicians and Nurses.** Seattle. Tues-Wed. Contact: U/W, Maria Lilja, (206) 543-1050.

May 5-6—**Health Effects of Synthetic Fibers.** Seattle. Thurs-Fri. Contact: U/W, (206) 543-1069.

May 13—**Current Drug Topics—Pharmacology for the Practitioner.** Seattle. Fri. Contact: VMMC.

May 19-20—**Update on Travel and International Medicine.** Seattle. Thurs-Fri. Contact: Maria Lilja, (206) 543-1050.

May 19-21—**Emergency Medicine Update.** Seattle. Thurs-Sat. Contact: VMMC.

May 26-27—**Alzheimer's Disease.** Seattle. Thurs-Fri. Contact: U/W, Maria Lilja, (206) 543-1050.

June 3—**Topics in General Internal Medicine.** Seattle. Fri. Contact: VMMC.

June 9—**Health Care and Anti-Trust.** Seattle. Thurs. Contact: U/W, Maria Lilja, (206) 543-1050.

June 9-10—**Update in Clinical Neurology.** Seattle. Thurs-Fri. Contact: Northwest Hospital, (206) 364-0500, Ext 1621.

June 9-11—**Obstetric Ultrasound.** Seattle. Thurs-Sat. Contact: Robin Murray, (202) 863-2543.

June 17-18—**Renal Disorders: Medical and Surgical Aspects.** Seattle. Fri-Sat. Contact: U/W, Maria Lilja, (206) 543-1050.

June 20-24—**Pathology of Lung Cancer.** Seattle. Mon-Fri. Contact: VMMC.

July 22-24—**First International Symposium on Pediatric Pain.** Seattle. Fri-Sun. Contact: U/W, Maria Lilja, (206) 543-1050.

July 29-31—**Seafair Anesthesia X.** Seattle. Fri-Sun. Contact: VMMC.

August 1-5—**Postgraduate Seminar in Psychology: Modern Approaches to Psychological Interviewing.** Ellensburg. Mon-Fri. Contact: Central Washington University, (509) 963-2381.

August 5—**Otology Update.** Seattle. Fri. Contact: VMMC.

August 8-14—**Summer Seminar in Medical Ethics and History.** Seattle. Mon-Sun. Contact: U/W, Maria Lilja, (206) 543-1050.

August 11-12—**Surviving the Elements.** Seattle. Thurs-Fri. Contact: U/W, Maria Lilja, (206) 543-1050.

August 29—**NW Regional Perinatal Conference: Current Issues in OB/GYN, Neonatology and Pediatrics.** Coeur d'Alene, Idaho. Thurs. Contact: (509) 624-3182.

August 31-September 3—**Second International Forum of Otorhinolaryngology.** Seattle. Wed-Sat. Contact: U/W, Maria Lilja, (206) 543-1050.

September 17-24—**Effective Management of Common Sports Injuries.** San Juan Islands. Sat-Sat. Contact: Kathy Rairigh, EPIC Expeditions, (208) 788-4995.

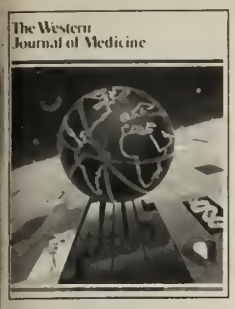
September 22-24—**Orthopedic Biomechanics.** Seattle. Thurs-Sat. Contact: VMMC.

WYOMING

June 23-26—**Wyoming Medical Society Annual Meeting.** Jackson Lake Lodge, Moran. Thurs-Sun. Contact: WMS, PO Drawer 4009, Cheyenne 82003-4009. (307) 635-2424.

July 17-22—**6th Annual Update in Clinical Microbiology and Immunology.** University of Utah Medical Center at Jackson Hole. Sun-Fri. 25 hrs. Contact: UUMC, 50 N. Medical Dr, Salt Lake City, UT 84132. (801) 581-2258. ◆

SPECIAL ISSUES



AIDS—A Global Perspective

The short and remarkable history of AIDS epidemiology began in 1981 with the description of the clinical syndrome in California and New York. In the 6 years that have followed, intensive epidemiologic studies have defined the mode of spread of AIDS and laid the foundation for current control efforts. Serosurveys and retrospective clinical studies have been used to trace the temporal origins of the pandemic prior to 1981, while prospective studies and an increasingly comprehensive worldwide surveillance system have provided more accurate data for the years following 1981. AIDS cases have now been reported and investigated throughout the world.

This issue, from the Special Programme on AIDS of the World Health Organization, considers the methods and limitations of AIDS case reporting and HIV serologic studies, summarizes modes of HIV transmission, defines geographic patterns of spread, and examines the epidemiology of HIV infections by continent.

—Jonathan M. Mann, MD
Director,
Special Programme on AIDS
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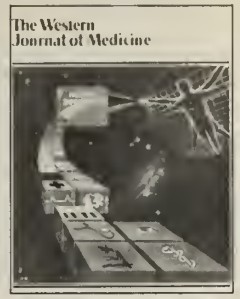

Medical Informatics

I would suggest that the computer in its relation to medicine is analogous to that of the microscope in the last century. . . . The analogous role that I believe the computer is now taking on is also that of a breakthrough tool—one enabling us to explore and better understand the informational and cognitive foundations of medicine. Its application to the classification and retrieval of data and to the management of information will result in a deeper insight into the structure of medical information and knowledge itself.

—Marsden S. Blois, PhD, MD

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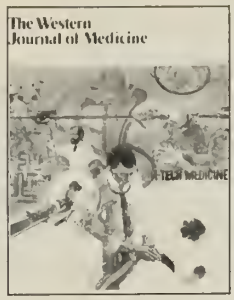

High-Tech Medicine

Progress in medical science seems to come in rushes. There are long periods of time during which we mainly fine-tune the status quo: third-generation drugs, better optics for endoscopes, more accurate assays, rapid development of x-ray film and so forth. Then, out of nowhere, a surge of new discoveries whose potential applications to medical practice seem limitless takes our breath away. We are now in such an epoch. Powerful and precise lasers. Almost unbelievable organ transplantation. Complex and uniquely informative magnetic resonance imaging and positron emission tomography. Exquisitely specific monoclonal antibodies. And the immense potential of modern molecular biology. This rush of new advances, collapsed into such a brief period of time, boggles the mind.

—R. Paul Robertson, MD

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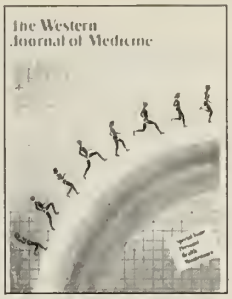

Personal Health Maintenance

The goal of this special issue is to provide an authoritative, current guide to disease prevention and health promotion. The contributors are distinguished experts in public health, epidemiology and clinical medicine.

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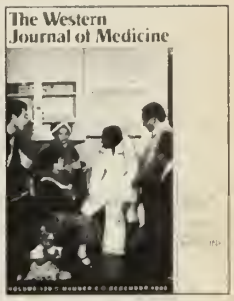

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—Malcolm S.M. Watts, MD

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E/O/E

PHYSICIANS WANTED

FAMILY PRACTITIONER. Visalia Medical Clinic has an opening for a BC/BE Family Practitioner to join a four physician department. Located in the San Joaquin Valley of California, serving a market area of approximately 350,000 citizens, the Visalia Medical Clinic is a 40 physician multispecialty clinic. Excellent hospital services and facilities. Compensation is incentive oriented with advancement to full partnership after one year. Excellent fringe benefits. John G. Heinsohn, Administrator, 5400 W. Hillsdale, Visalia, CA 93291; (209) 733-5222.

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DERMATOLOGIST. Visalia Medical Clinic has an opening for a BC/BE Dermatologist now staffed by one physician who has been with the Clinic for 15 years. Located in the San Joaquin Valley in central California and population approximately 350,000. Progressive city of 62,000, near national parks and the ocean. Compensation is incentive oriented with advancement to full partnership after one year. Excellent fringe benefits. If interested, CV to John G. Heinsohn, Administrator, 5400 W. Hillsdale, Visalia, CA 93291; (209) 733-5222.

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PHYSICIANS WANTED

CALIFORNIA. Emergency Medicine Faculty Positions. Immediate opportunities available for career-oriented Emergency Physicians who possess excellent clinical and teaching skills to join the faculty of Emergency Medicine department. BC in Family Practice, Internal Medicine, Surgery, and/or BE in Emergency Medicine. Our facility, located in southern California, averages 38,000 Emergency department visits per year, is a level II trauma center, regional burn center and neonatology intensive care center. These positions require a teaching commitment in a university-affiliated Family Practice training program. We offer a competitive remuneration package to include salary, malpractice insurance, time off, and flexible scheduling. Send CV to Empire Medical Group, PO Box 3571, San Bernardino, CA 92413.

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EMERGENCY GROUP seeking career oriented ACLS, ATLS physician for immediate opening. Moderate volume, income $120,000. Great outdoor activities including fishing, boating, skiing and sailing in south central Washington. Send CV to KEP, PO Box 6192, Kennewick, WA 99336; or call (509) 627-1798.

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FAMILY PRACTICE in four season playground. Live, work, and play in beautiful north Idaho. Excellent professional opportunity. Private practice affiliated with JCAH accredited hospital. For details call Nancy collect at (208) 784-1221, ext 304. Shoshone Medical Center, Jacobs Gulch, Kellogg, ID 83837.

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(Continued on Page 496)

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INFORMATION FOR AUTHORS

Submitting Manuscripts

Manuscripts for consideration should be sent to the editor, Malcolm S. M. Watts, MD, PO Box 7602, San Francisco, California 94120-7602. The transmittal letter should designate one person as correspondent and include complete address, with ZIP code and telephone number.

In view of *The Copyright Revision Act of 1976*, transmittal letters should contain the following language: "In consideration for reviewing and editing my submission, the author(s) undersigned hereby transfers, assigns, or otherwise conveys all copyright ownership to THE WESTERN JOURNAL OF MEDICINE in the event that such work is published by the journal." This statement should be signed by *all* authors.

Authors are urged to seek clarity and succinctness in all manuscripts regardless of subject matter or format and to give close attention to syntax, grammar, and spelling.

Clinical Investigation Section

Articles that authors wish to have considered for the Clinical Investigation section should be so designated in the transmittal letter. The type of articles appropriate for this section are those that describe experimental work in humans that extensively and prospectively examines scientific hypotheses relating to disease. An article describing a single case report will not normally be considered appropriate for this section.

Preparing Manuscripts

The original manuscript and *two* copies should be submitted on heavy bond paper (8½ by 11 inches, *not* erasable), typed *double-spaced throughout* (including legends, tables, and references) on one side of the paper, with 1½-inch margins. Articles should not exceed 3,000 words (less than 15 text pages typed double-spaced). Under exceptional circumstances only will articles longer than 4,000 words be published. Pages should be numbered consecutively, beginning with the title page. Manuscripts produced with a dot-matrix printer are ordinarily not acceptable.

Style

Abbreviations. Use of abbreviations should be minimized. If they are necessary, abbreviations should be spelled out at first mention, with the abbreviation itself immediately following in parentheses.

Weights and measures. Use Système International (SI) units throughout the manuscript. Provide metric equivalents for all SI units; they will be noted parenthetically in the published text.

Temperatures. Temperature readings should be given first in Celsius, followed by the Fahrenheit equivalent in parentheses.

Drug names. If the trade name of a drug is used, the generic name, including salt or ester, should be given first, followed by the trade name in parentheses. Trade names are capitalized, generic names are not.

Title Page

Titles are best when brief and concise. The title page should include the full name of the author(s), with degrees, academic or professional titles, complete addresses, and any institutional or other affiliations. The complete name and address of the person who will handle reprint requests also should appear on this page.

Abstract

The abstract (approximately 150 words) should be a short summary, saying in brief what is said at length in the body of the article—rather than such and such "is discussed," "is presented," or "was investigated."

Tables and Figures

Tables

Each table should be typed on a separate sheet of paper, be numbered consecutively in Arabic numerals, have a brief descriptive title, and have its position indicated in the text.

Illustrations (Figures)

Three sets of clear, unmounted black and white glossy prints of figures should be submitted (preferably 5 by 7 inches, but no larger than 8½ by 11 inches). For line drawings, original artwork or glossy prints are acceptable. Illustrations should be numbered consecutively in Arabic numerals and the position indicated in the text. Figure number, first author's name and top of the photo should be shown on the reverse side of each illustration. Recognizable photographs of patients are to be masked and written permission for publication obtained from the patients.

Legends

All legends for figures should be typed together on a separate sheet of paper. Magnification and stain for photomicrographs should be indicated in parentheses.

Permission for Reproduction

If an illustration or table has been used previously in another publication, written permission for its use must be obtained from the publisher and should accompany the manuscript. The source should be acknowledged in the legend if it can be done briefly by citation of a reference number. Otherwise, acknowledgment is made at the end of the figure legend or at the bottom of the table.

References

References should be limited to those cited in the text and should be to medical, scientific, or scholarly publications. (Mass circulation periodicals are referenced in parentheses in the text.) They must be typed double-spaced and numbered consecutively as they appear in the manuscript.* (See examples below for style.) Abbreviations of journal titles should conform to those used in *Index Medicus*.

Journal Articles

Note handling of multiple authorship. If more than three authors are listed as contributors, use "et al" to designate those names after the first three. Also note capitalization, punctuation, use of inclusive page numbers, and year of publication. Separate the subtitle from the title by either a dash or a colon. Use colon *only* if it appears in the original citation.

1. Jones JS, Anderson HW, Johnson DW, et al: The athletic heart revisited—Sudden death of a 28-year-old athlete. JAMA 1978; 292:444-456

2. Graybill JR, Alford RH, Smith RG, et al: Cell-mediated immunity in cryptococcosis: A brief review. Cell Immunol 1978; 7:76-79

Books

Note handling of "edition," "editor(s)," and "volume," as well as appropriate sequence of reference information and capitalization of chapters and titles.

3. Berne EJ, Smith TL: Role playing in therapy, chap 2, Principles of Group Therapy. New York, Oxford University Press, 1966, pp 35-51 *(author of chapter same as author of book)*

4. Munsung JM: The role of drugs, chap 2, *In* Brest AN, Mayer JH (Eds): Hypertension—Vol 2, Therapy, 2nd Ed. Springfield, Ill, Charles C Thomas, 1961, pp 456-479 *(author of chapter different from authors of book)*

Pamphlets, Monographs, or Books With No Given Author

5. AMA Department of Drugs: AMA Drug Evaluation, 3rd Ed. Littleton, Mass, Publishing Sciences Group, 1977 *(corporate author)*

6. Compilation of Standard Definitions, 3rd Ed. Philadelphia, American Society for Testing and Materials, 1976 *(no given author; give name and place of publisher)*

Articles in Press or Accepted for Publication

Any article accepted for publication should include the name of the journal (appropriately abbreviated) in which it will appear and the phrase "in press" or "accepted for publication" in place of the date of publication.

Personal Communications and Unpublished Data

This information should *not* be included in the reference list but should be given in parentheses in the body of the text. Date of communication, whether it was oral or written, and the person's name, highest academic degree, and professional affiliation should be provided.

**Exception:* Articles for Topics in Primary Care and Epitomes use a limited number of authoritative references, both to the specific topic and the subject as a whole, that are *not* cited in the text and are listed in alphabetic order.

Acknowledgments

It is the policy of the *WJM* not to print acknowledgments, the feeling being that if a person has contributed enough to a paper to be mentioned, he or she should be included among the authors, or the contribution should be mentioned in the body of the paper or in a footnote.

Correspondence

Brief manuscripts commenting on articles that have appeared in the journal, containing information of interest to physicians, or discussing issues of the day will be considered for publication. Very short reports of cases, clinical experience, clinical studies, adverse effects, and the like also will be considered. Items for the Correspondence section should not exceed 600 words and should have no more than five bibliographic references and one figure or table.

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Authors are responsible for all statements made in articles. Manuscripts are considered for publication with the explicit understanding that they are original, have not been published previously, and are not simultaneously under consideration by any other publication.

All accepted manuscripts are subject to copy editing, and authors are sent edited galleys for approval. No changes will be made after the final, edited version has been approved by the author.

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Revised 10/1/87

The World's Most Popular K*

Slow-K®

potassium chloride
slow-release tablets
8 mEq (600 mg)

It means "dependability" in almost any language

*Based on worldwide sales data on file, CIBA Pharmaceutical Company.
Capsule or tablet slow-release potassium chloride preparations should be reserved for patients who cannot tolerate, refuse to take, or have compliance problems with liquid or effervescent potassium preparations because of reports of intestinal and gastric ulceration and bleeding with slow-release KCl preparations.

Before prescribing, please consult Brief Prescribing Information on next page.

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C I B A

128-3568-A

The World's Most Popular K

For good reasons

- ☐ **It works**—a 12-year record of efficacy[1]
- ☐ **It's safe**—unsurpassed by any other KCl tablet or capsule[2]*
- ☐ **It's acceptable vs liquids**—greater palatability, fewer GI complaints, lower incidence of nausea[2]
- ☐ **It's comparable to 10 mEq**—in low-dosage supplementation[3]†
- ☐ **It's economical**—less expensive than all other leading KCl slow-release supplements on a per tablet cost to the patient[1]

Slow-K®
potassium chloride
slow-release tablets 8 mEq (600 mg)

For patients who can't or won't tolerate liquid KCl.

*The most common adverse reactions to potassium salts are gastrointestinal side effects.

†Pooled mean serum potassium following oral administration of 30 mEq K-Tab compared to 24 mEq Slow-K in diuretic-treated hypertensives (n = 20) over 8 weeks.

C I B A

References: 1. Data on file, CIBA Pharmaceutical Company. **2.** Skoutakis VA, Acchiardo SR, Wojciechowski NJ, et al: Liquid and solid potassium chloride: Bioavailability and safety. *Pharmacotherapy* 1980;4(6):392-397. **3.** Skoutakis VA, Carter CA, Acchiardo SR: Therapeutic assessment of Slow-K and K-Tab potassium chloride formulations in hypertensive patients treated with thiazide diuretics. *Drug Intell Clin Pharm* 1987;21:436-440

Slow-K®
potassium chloride USP
Slow-Release Tablets
8 mEq (600 mg)

BRIEF SUMMARY (FOR FULL PRESCRIBING INFORMATION SEE PACKAGE INSERT)

INDICATIONS AND USAGE
BECAUSE OF REPORTS OF INTESTINAL AND GASTRIC ULCERATION AND BLEEDING WITH SLOW-RELEASE POTASSIUM CHLORIDE PREPARATIONS, THESE DRUGS SHOULD BE RESERVED FOR THOSE PATIENTS WHO CANNOT TOLERATE OR REFUSE TO TAKE LIQUID OR EFFERVESCENT POTASSIUM PREPARATIONS OR FOR PATIENTS IN WHOM THERE IS A PROBLEM OF COMPLIANCE WITH THESE PREPARATIONS.
1. For therapeutic use in patients with hypokalemia with or without metabolic alkalosis; in digitalis intoxication and in patients with hypokalemic familial periodic paralysis.
2. For prevention of potassium depletion when the dietary intake of potassium is inadequate in the following conditions: patients receiving digitalis and diuretics for congestive heart failure; hepatic cirrhosis with ascites; states of aldosterone excess with normal renal function; potassium-losing nephropathy; and certain diarrheal states.
3. The use of potassium salts in patients receiving diuretics for uncomplicated essential hypertension is often unnecessary when such patients have a normal dietary pattern. Serum potassium should be checked periodically, however, and if hypokalemia occurs, dietary supplementation with potassium-containing foods may be adequate to control milder cases. In more severe cases supplementation with potassium salts may be indicated.

CONTRAINDICATIONS
Potassium supplements are contraindicated in patients with hyperkalemia, since a further increase in serum potassium concentration in such patients can produce cardiac arrest. Hyperkalemia may complicate any of the following conditions: chronic renal failure, systemic acidosis such as diabetic acidosis, acute dehydration, extensive tissue breakdown as in severe burns, adrenal insufficiency, or the administration of a potassium-sparing diuretic (e.g., spironolactone, triamterene) (see OVERDOSAGE).

All solid dosage forms of potassium supplements are contraindicated in any patient in whom there is cause for arrest or delay in tablet passage through the gastrointestinal tract. In these instances, potassium supplementation should be with a liquid preparation. Wax-matrix potassium chloride preparations have produced esophageal ulceration in certain cardiac patients with esophageal compression due to an enlarged left atrium.

WARNINGS
Hyperkalemia (See OVERDOSAGE).
In patients with impaired mechanisms for excreting potassium, the administration of potassium salts can produce hyperkalemia and cardiac arrest. This occurs most commonly in patients given potassium by the intravenous route but may also occur in patients given potassium orally. Potentially fatal hyperkalemia can develop rapidly and be asymptomatic.

The use of potassium salts in patients with chronic renal disease, or any other condition which impairs potassium excretion, requires particularly careful monitoring of the serum potassium concentration and appropriate dosage adjustment.

Interaction With Potassium-Sparing Diuretics
Hypokalemia should not be treated by the concomitant administration of potassium salts and a potassium-sparing diuretic (e.g., spironolactone or triamterene), since the simultaneous administration of these agents can produce severe hyperkalemia.

Gastrointestinal Lesions
Potassium chloride tablets have produced stenotic and/or ulcerative lesions of the small bowel and deaths. These lesions are caused by a high localized concentration of potassium ion in the region of a rapidly dissolving tablet, which injures the bowel wall and thereby produces obstruction, hemorrhage, or perforation. Slow-K is a wax-matrix tablet formulated to provide a controlled rate of release of potassium chloride and thus to minimize the possibility of a high local concentration of potassium ion near the bowel wall. While the reported frequency of small-bowel lesions is much less with wax-matrix tablets (less than one per 100,000 patient-years) than with enteric-coated potassium chloride tablets (40-50 per 100,000 patient-years) cases associated with wax-matrix tablets have been reported both in foreign countries and in the United States. In addition, perhaps because the wax-matrix preparations are not enteric-coated and release potassium in the stomach, there have been reports of upper gastrointestinal bleeding associated with these products. The total number of gastrointestinal lesions remains approximately one per 100,000 patient-years. Slow-K should be discontinued immediately and the possibility of bowel obstruction or perforation considered if severe vomiting, abdominal pain, distention, or gastrointestinal bleeding occurs.

Metabolic Acidosis
Hypokalemia in patients with metabolic acidosis should be treated with an alkalinizing potassium salt such as potassium bicarbonate, potassium citrate, or potassium acetate.

PRECAUTIONS
General:
The diagnosis of potassium depletion is ordinarily made by demonstrating hypokalemia in a patient with a clinical history suggesting some cause for potassium depletion. In interpreting the serum potassium level, the physician should bear in mind that acute alkalosis *per se* can produce hypokalemia in the absence of a deficit in total body potassium, while acute acidosis *per se* can increase the serum potassium concentration into the normal range even in the presence of a reduced total body potassium.

Information for Patients
Physicians should consider reminding the patient of the following:
To take each dose without crushing, chewing, or sucking the tablets.
To take this medicine only as directed. This is especially important if the patient is also taking both diuretics and digitalis preparations.
To check with the physician if there is trouble swallowing tablets or if the tablets seem to stick in the throat.
To check with the doctor at once if tarry stools or other evidence of gastrointestinal bleeding is noticed.

Laboratory Tests
Regular serum potassium determinations are recommended. In addition, during the treatment of potassium depletion, careful attention should be paid to acid-base balance, other serum electrolyte levels, the electrocardiogram, and the clinical status of the patient, particularly in the presence of cardiac disease, renal disease, or acidosis.

Drug Interactions
Potassium-sparing diuretics: see WARNINGS

Carcinogenesis, Mutagenesis, Impairment of Fertility
Long-term carcinogenicity studies in animals have not been performed.

Pregnancy Category C
Animal reproduction studies have not been conducted with Slow-K. It is also not known whether Slow-K can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Slow-K should be given to a pregnant woman only if clearly needed.

Nursing Mothers
The normal potassium ion content of human milk is about 13 mEq/L. It is not known if Slow-K has an effect on this content. Caution should be exercised when Slow-K is administered to a nursing woman.

Pediatric Use
Safety and effectiveness in children have not been established.

ADVERSE REACTIONS
One of the most severe adverse effects is hyperkalemia (see CONTRAINDICATIONS, WARNINGS, and OVERDOSAGE). There also have been reports of upper and lower gastrointestinal conditions including obstruction, bleeding, ulceration, and perforation (see CONTRAINDICATIONS and WARNINGS); other factors known to be associated with such conditions were present in many of these patients.

The most common adverse reactions to oral potassium salts are nausea, vomiting, abdominal discomfort, and diarrhea. These symptoms are due to irritation of the gastrointestinal tract and are best managed by taking the dose with meals or reducing the dose.

Skin rash has been reported rarely.

OVERDOSAGE
The administration of oral potassium salts to persons with normal excretory mechanisms for potassium rarely causes serious hyperkalemia. However, if excretory mechanisms are impaired or if potassium is administered too rapidly intravenously, potentially fatal hyperkalemia can result (see CONTRAINDICATIONS and WARNINGS). It is important to recognize that hyperkalemia is usually asymptomatic and may be manifested only by an increased serum potassium concentration (6.5-8.0 mEq/L) and characteristic electrocardiographic changes (peaking of T waves, loss of P wave, depression of S-T segment, and prolongation of the Q-T interval). Late manifestations include muscle paralysis and cardiovascular collapse from cardiac arrest (9-12 mEq/L).

Treatment measures for hyperkalemia include the following: (1) elimination of foods and medications containing potassium and of potassium-sparing diuretics; (2) intravenous administration of 300-500 ml/hr of 10% dextrose solution containing 10-20 units of insulin per 1,000 ml; (3) correction of acidosis, if present, with intravenous sodium bicarbonate; (4) use of exchange resins, hemodialysis, or peritoneal dialysis.

In treating hyperkalemia in patients who have been stabilized on digitalis, too rapid a lowering of the serum potassium concentration can produce digitalis toxicity.

DOSAGE AND ADMINISTRATION
The usual dietary intake of potassium by the average adult is 40-80 mEq per day. Potassium depletion sufficient to cause hypokalemia usually requires the loss of 200 or more mEq of potassium from the total body store. Dosage must be adjusted to the individual needs of each patient but is typically in the range of 20 mEq per day for the prevention of hypokalemia to 40-100 mEq or more per day for the treatment of potassium depletion. Large numbers of tablets should be given in divided doses.

Note: Slow-K slow-release tablets must be swallowed whole and never crushed, chewed, or sucked.

HOW SUPPLIED
Tablets—600 mg of potassium chloride (equivalent to 8 mEq) round, buff colored, sugar-coated (imprinted Slow-K)

Bottles of 100	NDC 0083-0165-30
Bottles of 1000	NDC 0083-0165-40
Consumer Pack—One Unit	
12 Bottles—100 tablets each	NDC 0083-0165-65
Accu-Pak® Unit Dose (Blister pack)	
Box of 100 (strips of 10)	NDC 0083-0165-32

Do not store above 86°F (30°C). Protect from moisture. Protect from light.

Dispense in tight, light-resistant container (USP).

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New Mexico Medical Society

102nd Annual Meeting
May 5-7, 1988

THURSDAY—May 5, 1988

7:00 a.m.	New Mexico Foundation for Medical Care Board of Directors Meeting
9:30 a.m.	New Mexico Physicians Mutual Liability Company Board of Directors Meeting
11:30 a.m.	New Mexico Physicians Mutual Liability Insurance Company—Annual Meeting
10:00 a.m. to 2:00 p.m.	**SEE FOR YOURSELF** A Community outreach project sponsored by the New Mexico Ophthalmological Society and the New Mexico Medical Society Public Relations Committee
1:00 p.m.	Scientific Session **AIDS—Reducing the Risk**
2:00 p.m.	New Mexico Medical Society Council Meeting
6:30 p.m.	Council Dinner—*Petroleum Club*

FRIDAY—May 6, 1988

8:30 a.m.	New Mexico Medical Society House of Delegates
9:45 a.m.	Reference Committee Hearings
10:00 a.m. to 2:00 p.m.	**SEE FOR YOURSELF**
12:00 noon	NEMPAC Luncheon
1:30 p.m.	Scientific Session **The Addictive Process and the New Mexico Medical Community**
6:30 p.m.	Past Presidents Club Dinner Meeting—*Tanoan Country Club* New Mexico Orthopaedic Association Dinner Meeting—*Petroleum Club*

SATURDAY—May 7, 1988

8:30 a.m.	New Mexico Physicians Mutual Liability Company **Risk Management Seminar**—First Session
1:30 p.m.	**Risk Management Seminar**—Second Session
4:30 p.m.	House of Delegates—Reconvene

For more information, please call or write:

New Mexico Medical Society
303 San Mateo Blvd, NE
Albuquerque, NM 87108
(505) 266-7868

FACULTY

Margaret (Garet) Bedrosian, MSW, LCSW

San Diego. Clinical Consultant to **Next Step,** a program designed to help children of alcoholics.

David A. Bennahum, MD

Albuquerque. Associate Professor, University of New Mexico School of Medicine.

Daniel R. Cameron, MD

Albuquerque. Vice-President, New Mexico Monitored Treatment Program.

Donald E. Fry, MD

Albuquerque. Chairman and Professor, Department of Surgery, University of New Mexico School of Medicine. American College of Surgeons Representative to Committee on AIDS, Centers for Disease Control.

Joan Gibson, PhD

Albuquerque. Adjunct Associate Professor, University of New Mexico Schools of Law and Medicine.

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Toby L. Simon, MD

Albuquerque. Medical Director, United Blood Services. Professor, Department of Pathology, Associate Professor, Department of Medicine, University of New Mexico School of Medicine. Chairman, Continuing Medical Education Committee, NMMS.

(Continued from Page 490)

PHYSICIANS WANTED

ARIZONA INTERNAL MEDICINE PHYSICIAN to associate with two man Internal Medicine group in Tucson. New office building with lab and x-ray. Well established practice. Sub-specialties welcome, BC/BE. Send CV to A. Oaks, 5265 E. Knight Dr, Tucson, AZ 85712.

CARDIOLOGIST. BC/BE sought to join a large hospital-based multispecialty clinic. University affiliated residency program. Excellent fringe benefits. Competitive salary. California license required. Send CV to Aung-Win Chiong, MD, The Permanente Medical Group, Inc, PO Box 254999, Sacramento, CA 95865-4999, or call (916) 973-5748. An Equal Opportunity Employer.

INTERNIST. Immediate opening for a BC/BE General Internist to join a 35 member multispecialty group located in San Luis Obispo on the central coast. Benefits include immediate shareholder status, retirement program, all practice costs paid, starting guaranteed salary plus strong incentive plan. Send CV to Recruitment, San Luis Medical Clinic, Ltd., 1235 Osos St, San Luis Obispo, CA 93401-3619.

CALIFORNIA, SONORA. Staff Physician position available in 11-12,000 visit ER in quaint, historic, growing gold country community with fantastic recreational opportunities, one hour from Yosemite. Excellent opportunity in an academic and democratic group. Send CV to Art B. Wong, MD, FACEP, EPMG, 1 Maritime Plaza, Ste 710, San Francisco, CA 94111.

FELLOWSHIP IN GERIATRIC MEDICINE. A unique fellowship in Geriatric Medicine is being offered beginning July 1, 1988, by a Fortune 100 company and a major university medical school in California. The program is two years in duration and provides the gamut of geriatric health care experience and qualifies one for the certificate examination in Geriatric Medicine. The fellowship stipend is attractive as are the working conditions in this unique experience. For further information please contact Number 86, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

PHYSICIANS WANTED. A General Surgeon and an Oncologist to join 16 physician multispecialty group with attached 40-bed hospital located in southern Idaho. Contact Business Administrator, Box 1233, Twin Falls, ID 83301.

NORTHERN CALIFORNIA rural community clinic seeks BC/BE Family Physician. Heart of the redwoods. Full range of practice, community hospital nearby. Contact Allan Katz, (707) 923-2783.

FAMILY PRACTICE. Rural Colorado. BC/BE Family Practitioner to join three Family Practitioners in growing multispecialty group. Excellent opportunity for person interested in rural living, mountain recreation, health care delivery for medically underserved populations. Send CV to Michael Bloom, 204 Carson Ave, Alamosa, CO 81101; (303) 589-5161.

FAMILY PHYSICIAN. BC/BE to join the Family Practice department of a busy, primary care based multispecialty group. Excellent opportunity for growth. Contact Shane Spray, Administrator, Skagit Valley Medical Center, 1400 E. Kincaid, Mt. Vernon, WA 98273; (206) 428-2524.

SOUTHERN CALIFORNIA

Enjoy professional challenge and growth with a successful and expanding HMO in southern California. CIGNA Healthplans of California is seeking Specialists and Primary Care physicians committed to concepts of prevention and health maintenance to join our facilities in Los Angeles and Orange Counties. We offer an excellent compensation and benefits package including profit sharing. For consideration, please forward CV to:

Director/Physician Recruitment
CIGNA Healthplans of California
505 N. Brand Blvd, Suite 400-49
Glendale, CA 91203

PHYSICIANS WANTED

PEDIATRICIAN position available with multispecialty group; BE/BC required; strong incentive plan; benefits included; retirement program and located in San Luis Obispo, California on the central coast. Send CV to Administration/Recruitment, San Luis Medical Clinic, 1235 Osos St, San Luis Obispo, CA 93401.

OTOLARYNGOLOGIST position available with multispecialty group; BE/BC required; strong incentive plan; benefits included; retirement program and located in San Luis Obispo, California on the central coast. Send CV to Administration/Recruitment, San Luis Medical Clinic, 1235 Osos St, San Luis Obispo, CA 93401.

CENTRAL OREGON community seeks BE/BC Internist. 103-bed combination facility has ICU/CCU. Service area of 12,000. Coverage available by Internal Medicine group in neighboring town. Generous practice assistance package. An outdoorsman's winter and summer paradise! Contact Jean Erickson, PROSEARCH, 305 NE 102nd Ave, Portland, OR 97220; (503) 256-2070.

NORTHWEST WASHINGTON STATE. BC/BE Internist with intensive care skills to join young solo Internist in very busy practice. Consultations and primary care. Beautiful location, recreational activities, excellent lifestyle. Send CV to Number 93, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

CARDIOLOGIST. The University of California, San Francisco and the Central California Faculty Medical Group seek a staff Cardiologist to join the teaching faculty at their affiliate, Valley Medical Center of Fresno. Applicants should be BC/BE. The scope of practice at VMC includes full invasive and non-invasive cardiology services. Geographic location offers a large population with a variety of cardiological diseases. VMC has 350 active beds and conducts residency training programs in most major clinical disciplines. The central California location offers enjoyable and affordable California living. Competitive salary and benefits. UCSF is an equal opportunity employer. Address inquiries to Lauren Grayson, MD, Chief of Cardiology, CCFMG, 2212 N. Winery, #130, Fresno, CA 93703; (209) 252-1835.

GENERAL SURGEON, BE/BC. Outstanding opportunity for aggressive Surgeon with a highly profitable, well-established, fee-for-service, multispecialty clinic. 14 physicians on staff. Ready made practice. Unmatchable guaranteed salary first year, then ownership. New hospital. Wonderful family town with nationally recognized school system and unequalled outdoor recreation possibilities. Telephone calls will not be accepted. Send CV to John Brust, Mesaba Clinic, 1814 14th Ave East, Hibbing, MN 55746.

GASTROENTEROLOGIST position available with multispecialty group; BE/BC required; strong incentive plan; benefits included; retirement program and located in San Luis Obispo, California on the central coast. Send CV to Administration/Recruitment, San Luis Medical Clinic, 1235 Osos St, San Luis Obispo, CA 93401.

INTERNIST/NEPHROLOGIST with special interest in teaching Internal Medicine for full-time appointment in university-affiliated, active teaching and clinical program with part-time Nephrology private practice. Inquiries, including CV, should be sent to M.B. Ross, MD, Chairman, Department of Medicine, San Bernardino County Medical Center, 780 E. Gilbert St, San Bernardino, CA 92404.

ORTHOPEDIC SURGEONS, BE/BC, general ortho or with spine, knee, hand, sports medicine fellowship, wanted for immediate openings in Sacramento, California, musculoskeletal specialty group. Guarantee, malpractice insurance, vacation first year, fee-for-service thereafter plus partnership opportunity. Interested physicians send CV to Number 91, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

PHYSICIANS WANTED

Physicians wanted for leading clinic

Prestigious Chicago-based clinic group specializing in the treatment of venous disorders is expanding nationally. Our newest clinics in Los Angeles, San Francisco, Seattle, San Diego and Phoenix are in need of physicians trained in internal medicine—or who have a broad base of medical experience. We will provide complete training in the latest proprietary techniques of treating venous disorders. We offer a six figure salary and bonus potential, along with malpractice insurance and health benefits. And since there are no weekend hours and a 40-hour work week, you will have plenty of leisure time. You won't have to worry about soliciting for patients or fighting insurance companies.

This is an outstanding opportunity for professional and financial advancement. If you are motivated to build a rewarding practice with the leader in the treatment of venous disorders, send your resume to:

Medical Director
Vein Clinics of America
2340 S. Arlington Heights Road
Arlington Heights, Illinois 60005

FAMILY PRACTITIONER position available with multispecialty group; BE/BC required; strong incentive plan; benefits included; retirement program and located in San Luis Obispo, California on the central coast. Send CV to Administration/Recruitment, San Luis Medical Clinic, 1235 Osos St, San Luis Obispo, CA 93401.

RADIOLOGIST needed part-time to read office x-rays for large musculoskeletal group in Sacramento, California. Fees negotiable. Send CV to Number 90, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

GENERAL INTERNIST position available with multispecialty group; BE/BC required; strong incentive plan; benefits included; retirement program and located in San Luis Obispo, California on the central coast. Send CV to Administration/Recruitment, San Luis Medical Clinic, 1235 Osos St, San Luis Obispo, CA 93401.

AGGRESSIVE, BC or recently Board eligible Internist needed for fee-for-service, multispecialty group. New, fully equipped, 150-bed hospital with heliport. The area has excellent recreational facilities and superb family environment with a nationally recognized school system. Subspecialty support is provided under a University of Minnesota affiliation. Send CV to Mesaba Clinic, 1814 14th Ave East, Hibbing, MN 55746; Attention: J. Brust.

(Continued on Page 502)

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IN HYPERTENSION

resistance in the elderly[1]

- ☐ Effective blood pressure control
- ☐ Low incidence of fatigue,[2,3] impotence[2,3] and cold extremities[2-4]

Contraindicated in bronchial asthma, overt cardiac failure, greater-than-first-degree heart block, cardiogenic shock, and severe bradycardia.

See next page for references and Brief Summary of Product Information, which includes a listing of reported adverse reactions.

TRANDATE® b.i.d.

labetalol HCl/Glaxo 100 mg/200 mg tablets

Because it also vasodilates

References: 1. Holtzman JL, Finley D, Johnson B, et al: The effects of single-dose atenolol, labetalol, and propranolol on cardiac and vascular function. *Clin Pharmacol Ther* 1986;40:268-273. 2. Due DL, Giguere GC, Plachetka JR. Postmarketing comparison of labetalol and propranolol in hypertensive patients. *Clin Ther* 1986;8(6) 624-631. 3. Burris JF, Goldstein J, Zager PG, et al: Comparative tolerability of labetalol versus propranolol, atenolol, pindolol, metoprolol, and nadolol. *J Clin Hypertens* 1986;3 1-9 4. Erb RJ, Plachetka JR. Thermographic evaluation of the peripheral vascular effects of labetalol and propranolol. *Curr Ther Res* 1985;28(1):68-73.

TRANDATE® Tablets
(labetalol hydrochloride)

BRIEF SUMMARY OF PRODUCT INFORMATION

The following is a brief summary only. Before prescribing, see complete prescribing information in TRANDATE® Tablets product labeling.

INDICATIONS AND USAGE: TRANDATE® Tablets are indicated in the management of hypertension. TRANDATE Tablets may be used alone or in combination with other antihypertensive agents, especially thiazide and loop diuretics.

CONTRAINDICATIONS: TRANDATE® Tablets are contraindicated in bronchial asthma, overt cardiac failure, greater-than-first-degree heart block, cardiogenic shock, and severe bradycardia (see **WARNINGS**).

WARNINGS: Cardiac Failure: Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure. Beta-blockade carries a potential hazard of further depressing myocardial contractility and precipitating more severe failure. Although beta-blockers should be avoided in overt congestive heart failure, if necessary labetalol HCl can be used with caution in patients with a history of heart failure who are well compensated. Congestive heart failure has been observed in patients receiving labetalol HCl. Labetalol HCl does not abolish the inotropic action of digitalis on heart muscle.

In Patients Without a History of Cardiac Failure: In patients with latent cardiac insufficiency, continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or be given a diuretic, and the response should be observed closely. If cardiac failure continues despite adequate digitalization and diuretic, TRANDATE® therapy should be withdrawn (gradually, if possible).

Exacerbation of Ischemic Heart Disease Following Abrupt Withdrawal: Angina pectoris has not been reported upon labetalol HCl discontinuation. However, hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy; exacerbation of angina and, in some cases, myocardial infarction have occurred after *abrupt* discontinuation of such therapy. When discontinuing chronically administered TRANDATE, particularly in patients with ischemic heart disease, the dosage should be gradually reduced over a period of one to two weeks and the patient should be carefully monitored. If angina markedly worsens or acute coronary insufficiency develops, TRANDATE administration should be reinstituted promptly, at least temporarily, and other measures appropriate for the management of unstable angina should be taken. Patients should be warned against interruption or discontinuation of therapy without the physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue TRANDATE therapy abruptly even in patients treated only for hypertension.

Nonallergic Bronchospasm (eg, Chronic Bronchitis and Emphysema): Patients with bronchospastic disease should, in general, not receive beta-blockers. TRANDATE may be used with caution, however, in patients who do not respond to, or cannot tolerate, other antihypertensive agents. It is prudent, if TRANDATE is used, to use the smallest effective dose, so that inhibition of endogenous or exogenous beta-agonists is minimized.

Pheochromocytoma: Labetalol HCl has been shown to be effective in lowering blood pressure and relieving symptoms in patients with pheochromocytoma. However, paradoxical hypertensive responses have been reported in a few patients with this tumor; therefore, use caution when administering labetalol HCl to patients with pheochromocytoma.

Diabetes Mellitus and Hypoglycemia: Beta-adrenergic blockade may prevent the appearance of premonitory signs and symptoms (eg, tachycardia) of acute hypoglycemia. This is especially important with labile diabetics. Beta-blockade also reduces the release of insulin in response to hyperglycemia; it may therefore be necessary to adjust the dose of antidiabetic drugs.

Major Surgery: The necessity or desirability of withdrawing beta-blocking therapy prior to major surgery is controversial. Protracted severe hypotension and difficulty in restarting or maintaining a heartbeat have been reported with beta-blockers. The effect of labetalol HCl's alpha-adrenergic activity has not been evaluated in this setting.

A synergism between labetalol HCl and halothane anesthesia has been shown (see **Drug Interactions** under **PRECAUTIONS**).

PRECAUTIONS: General: *Impaired Hepatic Function:* TRANDATE® Tablets should be used with caution in patients with impaired hepatic function since metabolism of the drug may be diminished.

Jaundice or Hepatic Dysfunction: On rare occasions, labetalol HCl has been associated with jaundice (both hepatic and cholestatic). It is therefore recommended that treatment with labetalol HCl be stopped immediately should a patient develop jaundice or laboratory evidence of liver injury. Both have been shown to be reversible on stopping therapy.

Information for Patients: As with all drugs with beta-blocking activity, certain advice to patients being treated with labetalol HCl is warranted. This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects. While no incidence of the abrupt withdrawal phenomenon (exacerbation of angina pectoris) has been reported with labetalol HCl, dosing with TRANDATE Tablets should not be interrupted or discontinued without a physician's advice. Patients being treated with TRANDATE Tablets should consult a physician at any sign of impending cardiac failure. Also, transient scalp tingling may occur, usually when treatment with TRANDATE Tablets is initiated (see **ADVERSE REACTIONS**).

Laboratory Tests: As with any new drug given over prolonged periods, laboratory parameters should be observed over regular intervals. In patients with concomitant illnesses, such as impaired renal function, appropriate tests should be done to monitor these conditions.

Drug Interactions: In one survey, 2.3% of patients taking labetalol HCl in combination with tricyclic antidepressants experienced tremor as compared to 0.7% reported to occur with labetalol HCl alone. The contribution of each of the treatments to this adverse reaction is unknown, but the possibility of a drug interaction cannot be excluded.

Drugs possessing beta-blocking properties can blunt the bronchodilator effect of beta-receptor agonist drugs in patients with bronchospasm; therefore, doses greater than the normal antiasthmatic dose of beta-agonist bronchodilator drugs may be required.

Cimetidine has been shown to increase the bioavailability of labetalol HCl. Since this could be explained either by enhanced absorption or by an alteration of hepatic metabolism of labetalol HCl, special care should be used in establishing the dose required for blood pressure control in such patients.

Synergism has been shown between halothane anesthesia and intravenously administered labetalol HCl. During controlled hypotensive anesthesia using labetalol HCl in association with halothane, high concentrations (3% or above) of halothane should not be used because the degree of hypotension will be increased and because of the possibility of a large reduction in cardiac output and an increase in central venous pressure. The anesthesiologist should be informed when a patient is receiving labetalol HCl.

Labetalol HCl blunts the reflex tachycardia produced by nitroglycerin without preventing its hypotensive effect. If labetalol HCl is used with nitroglycerin in patients with angina pectoris, additional antihypertensive effects may occur.

Drug/Laboratory Test Interactions: The presence of a metabolite of labetalol in the urine may result in falsely increased levels of urinary catecholamines when measured by a nonspecific trihydroxyindole (THI) reaction. In screening patients suspected of having a pheochromocytoma and being treated with labetalol HCl, specific radioenzymatic or high performance liquid chromatography assay techniques should be used to determine levels of catecholamines or their metabolites.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term oral dosing studies with labetalol HCl for 18 months in mice and for two years in rats showed no evidence of carcinogenesis. Studies with labetalol HCl using dominant lethal assays in rats and mice and exposing microorganisms according to modified Ames tests showed no evidence of mutagenesis.

Pregnancy: ***Teratogenic Effects: Pregnancy Category C:*** Teratogenic studies have been performed with

TRANDATE® Tablets (labetalol hydrochloride)

labetalol in rats and rabbits at oral doses up to approximately six and four times the maximum recommended human dose (MRHD), respectively. No reproducible evidence of fetal malformations was observed. Increased fetal resorptions were seen in both species at doses approximating the MRHD. There are no adequate and well-controlled studies in pregnant women. Labetalol should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects: Infants of mothers who were treated with labetalol HCl during pregnancy did not appear to be adversely affected by the drug. Oral administration of labetalol to rats during late gestation through weaning at doses of two to four times the MRHD caused a decrease in neonatal survival.

Labor and Delivery: Labetalol HCl given to pregnant women with hypertension did not appear to affect the usual course of labor and delivery.

Nursing Mothers: Small amounts of labetalol (approximately 0.004% of the maternal dose) are excreted in human milk. Caution should be exercised when TRANDATE Tablets are administered to a nursing woman.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: Most adverse effects are mild, transient, and occur early in the course of treatment. In controlled clinical trials of three to four months' duration, discontinuation of TRANDATE® Tablets due to one or more adverse effects was required in 7% of all patients. In these same trials, beta-blocker control agents led to discontinuation in 8% to 10% of patients, and a centrally acting alpha-agonist in 30% of patients.

The following adverse reactions were derived from multi-center, controlled clinical trials over treatment periods of three and four months. The rates, which ranged from less than 1% to 5% except as otherwise noted, are based on adverse reactions considered probably drug-related by the investigator. If all reports are considered, the rates are somewhat higher (eg, dizziness, 20%; nausea, 14%; fatigue, 11%).

Body as a Whole: Fatigue, asthenia, and headache.

Gastrointestinal: Nausea (6%), vomiting, dyspepsia, diarrhea, and taste distortion.

Central and Peripheral Nervous Systems: Dizziness (11%), paresthesia, and drowsiness.

Autonomic Nervous System: Nasal stuffiness, ejaculation failure, impotence, and increased sweating.

Cardiovascular: Edema and postural hypotension.

Respiratory: Dyspnea.

Skin: Rash.

Special Senses: Vision abnormality and vertigo.

The adverse effects were reported spontaneously and are representative of the incidence of adverse effects that may be observed in a properly selected hypertensive patient population, ie, a group excluding patients with bronchospastic disease, overt congestive heart failure, or other contraindications to beta-blocker therapy.

Clinical trials also included studies utilizing daily doses up to 2,400 mg in more severely hypertensive patients. The US therapeutic trials data base for adverse reactions that are clearly or possibly dose-related shows that the following side effects increased with increasing dose: dizziness, fatigue, nausea, vomiting, dyspepsia, paresthesia, nasal stuffiness, ejaculation failure, impotence, and edema.

In addition, a number of other less common adverse events have been reported in clinical trials or the literature:

Cardiovascular: Postural hypotension, including rarely, syncope.

Central and Peripheral Nervous Systems: Paresthesias, most frequently described as scalp tingling. In most cases, it was mild, transient, and usually occurred at the beginning of treatment.

Collagen Disorders: Systemic lupus erythematosus; positive antinuclear factor (ANF).

Eyes: Dry eyes.

Immunological System: Antimitochondrial antibodies.

Liver and Biliary System: Cholestasis with or without jaundice.

Musculoskeletal System: Muscle cramps; toxic myopathy.

Respiratory System: Bronchospasm.

Skin and Appendages: Rashes of various types, such as generalized maculopapular, lichenoid, urticarial, bullous lichen planus, psoriaform, and facial erythema; Peyronie's disease; reversible alopecia.

Urinary System: Difficulty in micturition, including acute urinary bladder retention.

Following approval for marketing in the United Kingdom, a monitored release survey involving approximately 6,800 patients was conducted for further safety and efficacy evaluation of this product. Results of this survey indicate that the type, severity, and incidence of adverse effects were comparable to those cited above.

Potential Adverse Effects: In addition, other adverse effects not listed above have been reported with other beta-adrenergic blocking agents.

Central Nervous System: Reversible mental depression progressing to catatonia, an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance or neuropsychometrics.

Cardiovascular: Intensification of AV block (see **CONTRAINDICATIONS**).

Allergic: Fever combined with aching and sore throat; laryngospasm; respiratory distress.

Hematologic: Agranulocytosis; thrombocytopenic or nonthrombocytopenic purpura.

Gastrointestinal: Mesenteric artery thrombosis; ischemic colitis.

The oculomucocutaneous syndrome associated with the beta-blocker practolol has not been reported with labetalol HCl.

Clinical Laboratory Tests: There have been reversible increases of serum transaminases in 4% of patients treated with labetalol HCl and tested, and more rarely, reversible increases in blood urea.

OVERDOSAGE: Information concerning possible overdosage and its treatment appears in the full prescribing information.

DOSAGE AND ADMINISTRATION: DOSAGE MUST BE INDIVIDUALIZED. The recommended *initial* dosage is 100 mg *twice* daily whether used alone or added to a diuretic regimen. After two or three days, using standing blood pressure as an indicator, dosage may be titrated in increments of 100 mg bid every two or three days. The usual *maintenance* dosage of labetalol HCl is between 200 and 400 mg *twice* daily. Before use, see complete prescribing information for dosage details.

HOW SUPPLIED: TRANDATE® Tablets, 100 mg, light orange, round, scored, film-coated tablets engraved on one side with "TRANDATE 100 GLAXO," bottles of 100 (NDC 0173-0346-43) and 500 (NDC 0173-0346-44) and unit dose packs of 100 tablets (NDC 0173-0346-47).

TRANDATE Tablets, 200 mg, white, round, scored, film-coated tablets engraved on one side with "TRANDATE 200 GLAXO," bottles of 100 (NDC 0173-0347-43) and 500 (NDC 0173-0347-44) and unit dose packs of 100 tablets (NDC 0173-0347-47).

TRANDATE Tablets, 300 mg, peach, round, scored, film-coated tablets engraved on one side with "TRANDATE 300 GLAXO," bottles of 100 (NDC 0173-0348-43) and 500 (NDC 0173-0348-44) and unit dose packs of 100 tablets (NDC 0173-0348-47).

TRANDATE Tablets should be stored between 2° and 30°C (36° and 86°F). TRANDATE Tablets in the unit dose boxes should be protected from excessive moisture.

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September 1986

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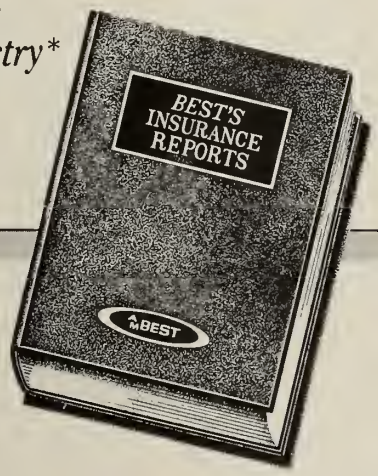

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(Continued from Page 496)

PHYSICIANS WANTED

STAFF PHYSICIAN II/ STAFF PHYSICIAN SPECIALIST & PHYSICIAN EPIDEMIOLOGIST

Santa Barbara County Health Care Services Staff Physician will serve as Director of Preventive Medicine Services. Responsible for communicable disease control and surveillance including TB, STD, immunizations; general supervision of AIDS Services Division including preventive, educational, and testing services; general supervision of Child Health, Vital Statistics, Public Health Laboratory, and Family Planning; preparation and planning of budgets, grant applications, reports; input into policy development, consultant/liaison to community with preventive medicine issues. Requires California license as a Physician and Surgeon and three years medical experience after residency at II level and license and certification from American Specialty Board at the Specialist level. Seeking strong leadership, planning, organizational, and staff development skills. Salary $70,276/II, $80,664/Specialist (position to be filled at either level).

Physician Epidemiologist (contract position available immediately) will be responsible for planning, implementation, and evaluation of investigation of specific disease entities; integration of findings into health policies; supervision of professional, technical, and clerical staff; provide expert consultation on epidemiology to state and local programs/organizations; acts as liaison between department and medical institutions/agencies cooperating in studies of mutual interest; coordination of activities of advisory committee; preparation and planning of budgets, grant applications, reports. Requires California license as a Physician/Surgeon and five years experience. Administration/public health experience preferred for both positions. Salary negotiable. *Need only submit résumé for Epidemiologist and must obtain and submit county application for Staff Physician.*

Santa Barbara County Personnel Department
1226 Anacapa St, Santa Barbara, CA 93101
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Affirmative Action/Equal Opportunity Employer

VENTURA (Ventura County). Multispecialty group of 35 physicians has immediate position available for BC/BE Family Practitioner. This opening is located in the Immediate Care department. The growth oriented group is located on the California coast, 60 miles north of Los Angeles. Guaranteed salary plus incentives. No investment required. City is a great place to raise a family in a clean environment. Send résumé to Recruitment, Family Practice, 2705 Loma Vista Rd, Ventura, CA 93003.

NEW MEXICO. BC/BE Primary Care Physician for 500-bed Psychiatric/Geriatric hospital. Exciting programs in an exciting location, with superb climate, recreational, and cultural benefits. Base salary $70,017 plus optional on-call salary supplement to $10,000. Fringe benefits are 21%, including paid malpractice and license fees, 2.5% per year retirement. Contact Philip Taulbee, MD, Medical Director, Las Vegas Medical Center, Box 1388, Las Vegas, NM 87701; (505) 454-2401.

PEDIATRICIAN, BC/BE. Interest in Neonatology preferred. Attractive salary and benefits. Partnership available in two years. Busy practice in agricultural community one-and-one-half hours from San Diego, California. Reply with CV to Drs Mirza R. Baig and Mohammad I. Admani, PO Box 590, El Centro, CA 92243.

IDAHO. Enjoy the great outdoors and an active, interesting Family Practice, including Obstetrics. Join four physicians and nine nurse practitioners working in rural community health centers near Boise. Emphasis on prevention. Good specialist back-up. Available now. Contact Erwin Teuber, Administrator, or Peter Barnett, MD, Medical Director, Terry Reilly Health Services, 211 16th Avenue North, Nampa, ID 83651; (208) 467-4431.

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NEED ASSOCIATE IN INTERNAL MEDICINE OR FAMILY PRACTICE

. . . for excellent west Orange County location. Large, well equipped office. Terms negotiable.

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CAMARILLO (Ventura County). Multispecialty group of 35 physicians has immediate positions available for BC/BE Family Practitioner. This opening is located in the Camarillo satellite with the main facility located in Ventura. The growth oriented group is located on the California coast, 60 miles north of Los Angeles. Guaranteed salary plus incentives. No investment required. City is a great place to raise a family in a clean environment. Send résumé to Recruitment, Family Practice, 2705 Loma Vista Rd, Ventura, CA 93003.

ESTABLISHED BC FAMILY PRACTITIONER in south central Washington seeks BE/BC associate with OB interest. Practice in rural, family-oriented community serving area of 45,000. Income guarantee and assistance with relocation. Ski at White Pass. Fishing and other water sports on nearby Rimrock Lake and Columbia River. Contact PROSEARCH, 305 NE 102nd Ave, Portland, OR 97220; (503) 256-2070, ext 202.

SOUTH CENTRAL WASHINGTON COMMUNITY seeks BE/BC Internist for solo practice. Share office space with two other physicians. First year income guarantee and other assistance. Great income potential for right candidate! Progressive 38-bed hospital has CT services. Excellent schools and recreation. Contact PROSEARCH, 305 NE 102nd Ave, Portland, OR 97220; (503) 256-4488.

VENTURA (Ventura County). Multispecialty group of 35 physicians has immediate positions available for BC/BE General Internists. The growth oriented group is located on the California coast, 60 miles north of Los Angeles. Guaranteed salary plus incentives. No investment required. City is a great place to raise a family in a clean environment. Send résumé to Recruitment, General Internists, 2705 Loma Vista Rd, Ventura, CA 93003.

INTERNIST with interest in trauma, Cardiology, or Gastroenterology, also willing to practice general Internal Medicine in a prosperous family-oriented community in southeastern New Mexico. Please submit CV to Rita Longino, Southwest Community Health Services, PO Box 26666, Albuquerque, NM 87125-6666; or call 1 (800) 545-4030, ext 8300.

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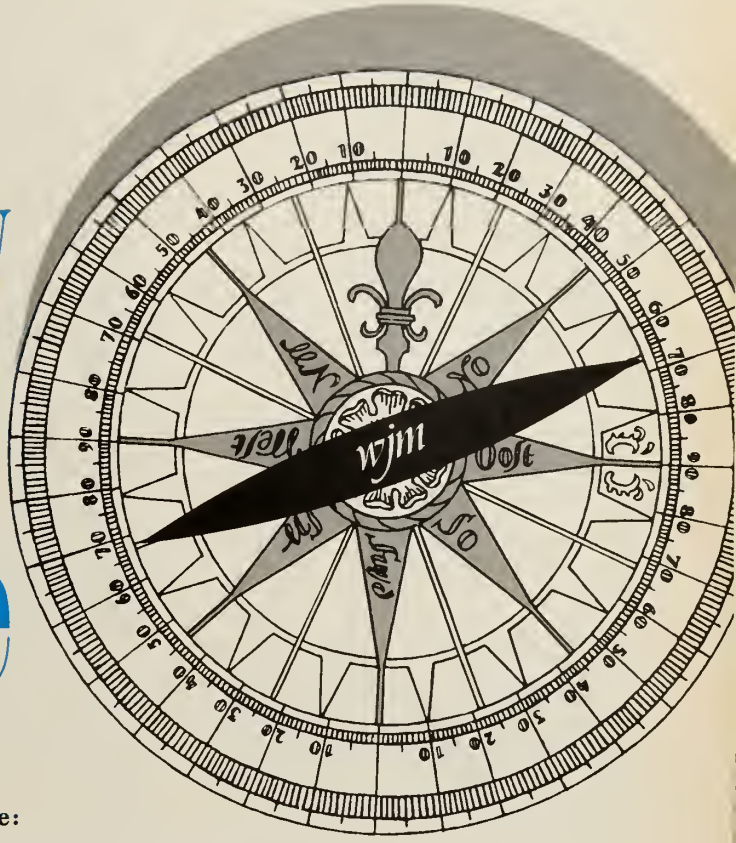

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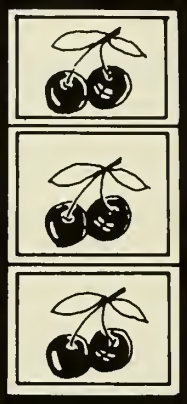

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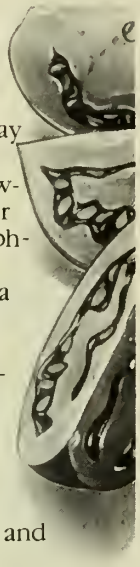

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California Medical Association—PO Box 7690, San Francisco 94120-7690. (415) 541-0900. Annual Meeting: March 3-8, 1989, Disneyland Hotel, Anaheim.

Colorado Medical Society—PO Box 17550, Denver 80217-0550. (303) 779-5455. Annual Meeting: September 15-17, 1988, Marriott City Center, Denver.

Hawaii Medical Association—320 Ward Ave, Suite 200, Honolulu 96814. (808) 536-7702. Annual Meeting: October 10-12, 1987, Kauai Surf, Kauai.

Idaho Medical Association—305 W Jefferson, PO Box 2668, Boise 83701. (208) 344-7888. Annual Meeting: July 21-23, 1988, Sun Valley.

Montana Medical Association—2012 11th Ave, Suite 12, Helena 59601. (406) 443-4000. Annual Meeting: September 29-October 1, 1988, Heritage Inn, Great Falls.

Nevada State Medical Association—3660 Baker Lane, Reno 89502. (702) 825-6788. Annual Meeting: April 21-24, 1988, Laughlin.

New Mexico Medical Society—303 San Mateo NE, Suite 204, Albuquerque 87108. (505) 266-7868. Annual Meeting: May 5-7, 1988, Hilton Inn, Albuquerque.

Oregon Medical Association—5210 SW Corbett Ave, Portland 97201. (503) 226-1555. Annual Meeting: (House of Delegates only): November 6-8, 1987, Portland.

Utah Medical Association—540 E Fifth South, Salt Lake City 84102. (801) 355-7477. Annual Meeting: September 21-23, 1988, University Park Hotel, Salt Lake City.

Washington State Medical Association—900 United Airlines Bldg, 2033 6th Ave, Seattle 98121. (206) 441-WSMA. Annual Meeting: September 15-18, 1988, Yakima.

Wyoming Medical Society—PO Drawer 4009, Cheyenne 82003-4009. (307) 635-2424. Annual Meeting: June 23-26, 1988, Jackson Lake Lodge, Moran.

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BACTRIM™ (trimethoprim and sulfamethoxazole/Roche)

Before prescribing, please consult complete product information, a summary of which follows:

CONTRAINDICATIONS: Hypersensitivity to trimethoprim or sulfonamides, documented megaloblastic anemia due to folate deficiency, pregnancy at term and during the nursing period; infants less than two months of age

WARNINGS: **FATALITIES ASSOCIATED WITH THE ADMINISTRATION OF SULFONAMIDES, ALTHOUGH RARE, HAVE OCCURRED DUE TO SEVERE REACTIONS, INCLUDING STEVENS-JOHNSON SYNDROME, TOXIC EPIDERMAL NECROLYSIS, FULMINANT HEPATIC NECROSIS, AGRANULOCYTOSIS, APLASTIC ANEMIA AND OTHER BLOOD DYSCRASIAS.**

BACTRIM SHOULD BE DISCONTINUED AT THE FIRST APPEARANCE OF SKIN RASH OR ANY SIGN OF ADVERSE REACTION. Clinical signs, such as rash, sore throat, fever, pallor, purpura or jaundice, may be early indications of serious reactions In rare instances a skin rash may be followed by more severe reactions, such as Stevens-Johnson syndrome, toxic epidermal necrolysis, hepatic necrosis or serious blood disorder Perform complete blood counts frequently

BACTRIM SHOULD NOT BE USED IN THE TREATMENT OF STREPTOCOCCAL PHARYNGITIS Clinical studies show that patients with group A β-hemolytic streptococcal tonsillopharyngitis have a greater incidence of bacteriologic failure when treated with Bactrim than with penicillin

PRECAUTIONS; *General* Give with caution to patients with impaired renal or hepatic function, possible folate deficiency (e g , elderly, chronic alcoholics, patients on anticonvulsants, with malabsorption syndrome, or in malnutrition states) and severe allergies or bronchial asthma In glucose-6-phosphate dehydrogenase deficient individuals, hemolysis may occur, frequently dose-related

Use in the Elderly May be increased risk of severe adverse reactions in elderly, particularly with complicating conditions, *e g* , impaired kidney and/or liver function, concomitant use of other drugs Severe skin reactions, generalized bone marrow suppression (see WARNINGS and ADVERSE REACTIONS) or a specific decrease in platelets (with or without purpura) are most frequently reported severe adverse reactions in elderly In those concurrently receiving certain diuretics, primarily thiazides, increased incidence of thrombocytopenia with purpura reported Make appropriate dosage adjustments for patients with impaired kidney function (see DOSAGE AND ADMINISTRATION).

Use in the Treatment of Pneumocystis Carinii *Pneumonitis in Patients with Acquired Immunodeficiency Syndrome (AIDS)* Because of unique immune dysfunction, AIDS patients may not tolerate or respond to Bactrim in same manner as non-AIDS patients Incidence of side effects, particularly rash, fever, leukopenia, with Bactrim in AIDS patients treated for *Pneumocystis carinii* pneumonitis reported to be greatly increased compared with incidence normally associated with Bactrim in non-AIDS patients

Information for Patients Instruct patients to maintain adequate fluid intake to prevent crystalluria and stone formation

Laboratory Tests Perform complete blood counts frequently; if a significant reduction in the count of any formed blood element is noted, discontinue Bactrim Perform urinalyses with careful microscopic examination and renal function tests during therapy, particularly for patients with impaired renal function

Drug Interactions In elderly patients concurrently receiving certain diuretics, primarily thiazides, an increased incidence of thrombocytopenia with purpura has been reported Bactrim may prolong the prothrombin time in patients who are receiving the anticoagulant warfarin Keep this in mind when Bactrim is given to patients already on anticoagulant therapy and reassess coagulation time Bactrim may inhibit the hepatic metabolism of phenytoin Given at a common clinical dosage, it increased the phenytoin half-life by 39% and decreased the phenytoin metabolic clearance rate by 27% When giving these drugs concurrently, be alert for possible excessive phenytoin effect Sulfonamides can displace methotrexate from plasma protein binding sites, thus increasing free methotrexate concentrations

Drug/Laboratory Test Interactions Bactrim, specifically the trimethoprim component, can interfere with a serum methotrexate assay as determined by the competitive binding protein technique (CBPA) when a bacterial dihydrofolate reductase is used as the binding protein No interference occurs if methotrexate is measured by a radioimmunoassay (RIA) The presence of trimethoprim and sulfamethoxazole may also intertere with the Jaffe alkaline picrate reaction assay for creatinine, resulting in overestimations of about 10% in the range of normal values

Carcinogenesis, Mutagenesis, Impairment of Fertility *Carcinogenesis* Long-term studies in animals to evaluate carcinogenic potential not conducted with Bactrim *Mutagenesis* Bacterial mutagenic studies not performed with sulfamethoxazole and trimethoprim in combination Trimethoprim demonstrated to be nonmutagenic in the Ames assay No chromosomal damage observed in human leukocytes *in vitro* with sulfamethoxazole and trimethoprim alone or in combination, concentrations used exceeded blood levels of these compounds following therapy with Bactrim Observations of leukocytes obtained from patients treated with Bactrim revealed no chromosomal abnormalities *Impairment of Fertility* No adverse effects on fertility or general reproductive performance observed in rats given oral dosages as high as 70 mg/kg/day trimethoprim plus 350 mg/kg/day sulfamethoxazole

Pregnancy Teratogenic Effects Pregnancy Category C Trimethoprim and sulfamethoxazole may interfere with folic acid metabolism, use during pregnancy only if potential benefit justifies potential risk to fetus Nonteratogenic Effects See CONTRAINDICATIONS section

Nursing Mothers See CONTRAINDICATIONS section

Pediatric Use Not recommended for infants under two months (see INDICATIONS and CONTRAINDICATIONS sections)

ADVERSE REACTIONS: Most common are gastrointestinal disturbances (nausea, vomiting, anorexia) and allergic skin reactions (such as rash and urticaria) **FATALITIES ASSOCIATED WITH THE ADMINISTRATION OF SULFONAMIDES, ALTHOUGH RARE, HAVE OCCURRED DUE TO SEVERE REACTIONS, INCLUDING STEVENS-JOHNSON SYNDROME, TOXIC EPIDERMAL NECROLYSIS, FULMINANT HEPATIC NECROSIS, AGRANULOCYTOSIS, APLASTIC ANEMIA AND OTHER BLOOD DYSCRASIAS (SEE WARNINGS SECTION)**

Hematologic Agranulocytosis, aplastic anemia, thrombocytopenia, leukopenia, neutropenia, hemolytic anemia, megaloblastic anemia, hypoprothrombinemia, methemoglobinemia, eosinophilia *Allergic Reactions* Stevens-Johnson syndrome, toxic epidermal necrolysis, anaphylaxis, allergic myocarditis, erythema multiforme, exfoliative dermatitis, angioedema, drug fever, chills, Henoch-Schoenlein purpura, serum sickness-like syndrome, generalized allergic reactions, generalized skin eruptions, photosensitivity, conjunctival and scleral injection, pruritus, urticaria and rash Periarteritis nodosa and systemic lupus erythematosus have been reported *Gastrointestinal* Hepatitis (including cholestatic jaundice and hepatic necrosis), elevation of serum transaminase and bilirubin, pseudomembranous enterocolitis, pancreatitis, stomatitis, glossitis, nausea, emesis, abdominal pain, diarrhea, anorexia *Genitourinary* Renal failure, interstitial nephritis, BUN and serum creatinine elevation, toxic nephrosis with oliguria and anuria, crystalluria *Neurologic* Aseptic meningitis, convulsions, peripheral neuritis, ataxia, vertigo, tinnitus, headache *Psychiatric* Hallucinations, depression, apathy, nervousness. *Endocrine* Sulfonamides bear certain chemical similarities to some goitrogens, diuretics (acetazolamide and the thiazides) and oral hypoglycemic agents, cross-sensitivity may exist Diuresis and hypoglycemia have occurred rarely in patients receiving sulfonamides *Musculoskeletal* Arthralgia, myalgia *Miscellaneous* Weakness, fatigue, insomnia

DOSAGE AND ADMINISTRATION: **Not recommended for use in infants less than two months of age.**

URINARY TRACT INFECTIONS AND SHIGELLOSIS IN ADULTS AND CHILDREN, AND ACUTE OTITIS MEDIA IN CHILDREN *Usual adult* dosage for urinary tract infections is one DS tablet, two tablets or four teaspoonfuls (20 ml) *b i d* for 10 to 14 days. Use identical daily dosage for 5 days for shigellosis *Recommended dosage for children* with urinary tract infections or acute otitis media is 8 mg/kg trimethoprim and 40 mg/kg sulfamethoxazole per 24 hours, in two divided doses every 12 hours for 10 days Use identical daily dosage for 5 days for shigellosis *Renal Impaired* Creatinine clearance above 30 ml/min, give usual dosage, 15-30 ml/min, give one-half the usual regimen; below 15 ml/min, use not recommended

ACUTE EXACERBATIONS OF CHRONIC BRONCHITIS IN ADULTS Usual adult dosage is one DS tablet, two tablets or four teasp (20 ml) *b i d* for 14 days

PNEUMOCYSTIS CARINII PNEUMONITIS Recommended dosage is 20 mg/kg trimethoprim and 100 mg/kg sulfamethoxazole per 24 hours in equal doses every 6 hours for 14 days See complete product information for suggested children's dosage table

HOW SUPPLIED: *DS (double strength) Tablets* (160 mg trimethoprim and 800 mg sulfamethoxazole)—bottles of 100, 250 and 500, Tel-E-Dose* packages of 100, Prescription Paks of 20 *Tablets* (80 mg trimethoprim and 400 mg sulfamethoxazole)—bottles of 100 and 500, Tel-E-Dose* packages of 100; Prescription Paks of 40 *Pediatric Suspension* (40 mg trimethoprim and 200 mg sulfamethoxazole per teasp)—bottles of 100 ml and 16 oz (1 pint) *Suspension* (40 mg trimethoprim and 200 mg sulfamethoxazole per teasp)—bottles of 16 oz (1 pint)

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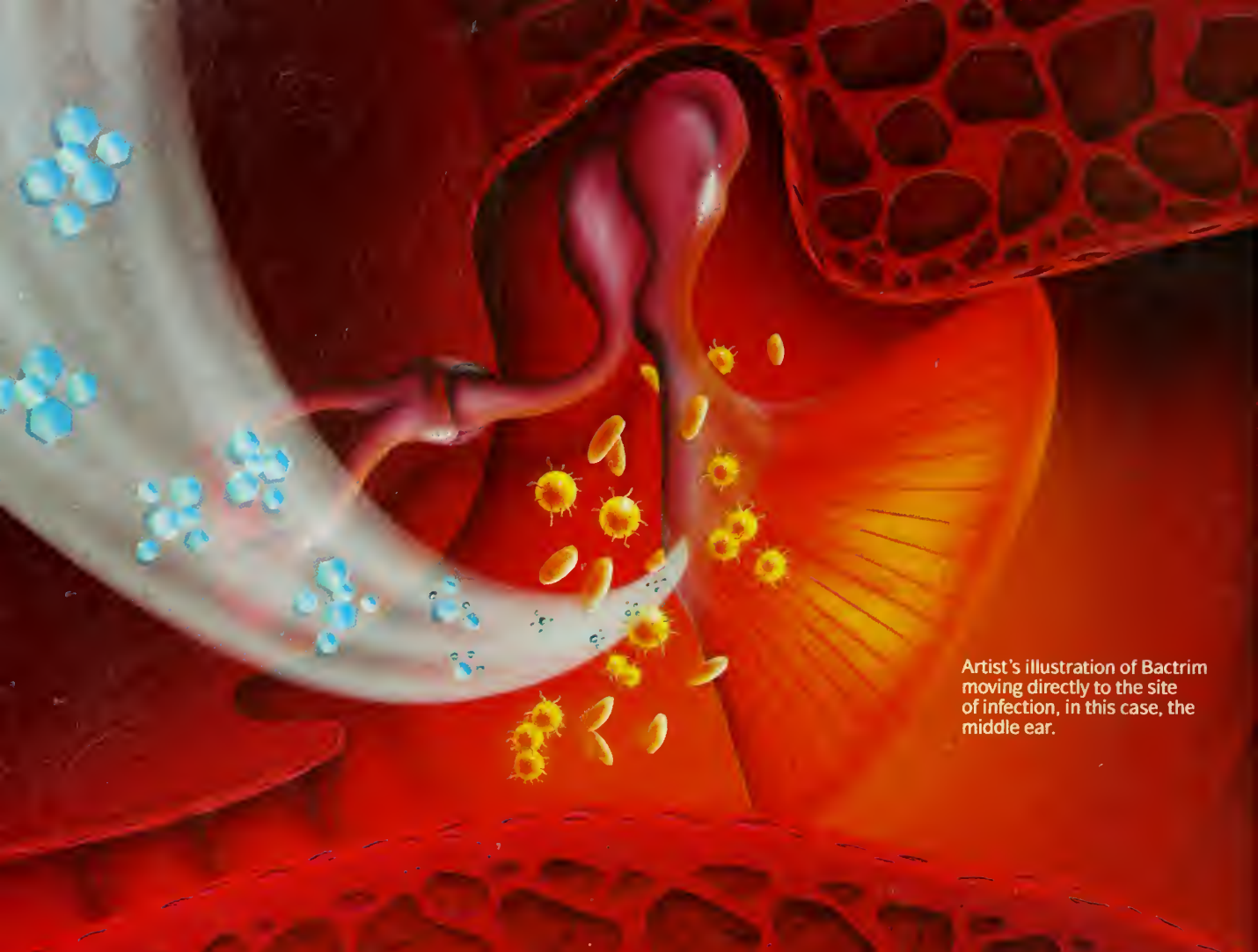

Artist's illustration of Bactrim moving directly to the site of infection, in this case, the middle ear.

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In vitro results may not correlate with clinical results. Not indicated for prophylactic or prolonged use in otitis media and contraindicated in infants under two months of age.

Specify. Do Not Substitute.

Bactrim™ Pediatric

(40 mg trimethoprim and 200 mg sulfamethoxazole per 5 ml)

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COURSE OBJECTIVES

This course focuses on three critical areas in cardiology—congestive heart failure, ventricular arrhythmias, and cardiovascular pharmacology—updating and improving the physician's understanding in the following areas:

Management strategies for congestive heart failure, including use of phosphodiesterase inhibitors, vasodilators, angiotensin-converting enzymes, surgery, and the recently discovered peptide, atrial natriuretic factor.

Guidelines for managing ventricular arrhythmias, including the comparative risks of premature ventricular contractions and nonsustained or sustained ventricular tachycardia, with specific diagnostic techniques for each, and advice on using the new antiarrhythmic agents—tocainide, mexiletine, flecainide, and amiodarone.

Review of what's new in cardiovascular pharmacology, including beneficial and adverse effects associated with some of the newer cardiovascular drugs, tips for dealing with hypertensive emergencies, the pros and cons of streptokinase therapy, and what can be expected from therapy with tissue plasminogen activator (t-PA).

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PROGRAM I—THE FAILING HEART

Management Strategies for Congestive Heart Failure
H. Jeremy Swan, M.D., Professor of Medicine, University of California, Los Angeles, School of Medicine, and Director, Division of Cardiology, Cedars-Sinai Medical Center, Los Angeles.

Ace Inhibitors and Atrial Natriuretic Peptides for Treatment of Congestive Heart Failure
John C. Burnett, M.D., Assistant Professor of Medicine and Physiology, Mayo Medical School, Rochester.
(Original Issue IM 35/2)

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David G. Benditt, M.D., Associate Professor of Medicine, University of Minnesota Medical School, Minneapolis.

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(Original Issue IM 34/14)

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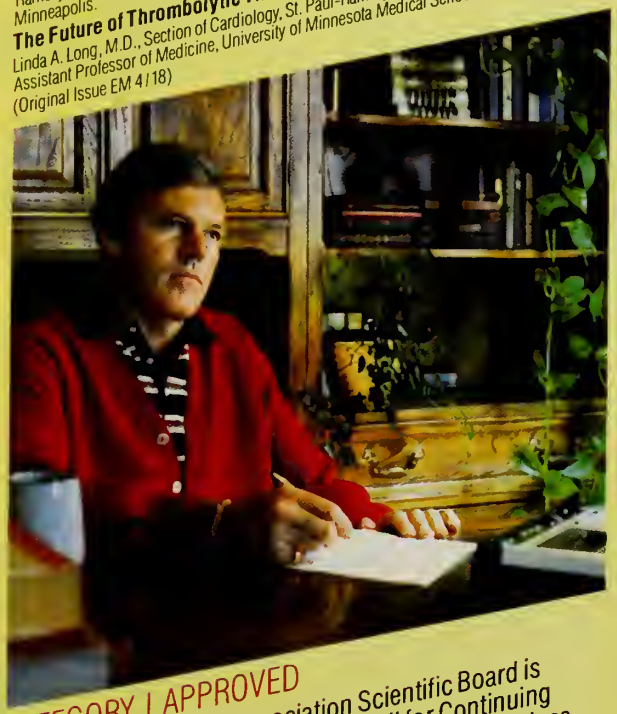
Linda A. Long, M.D., Section of Cardiology, St. Paul-Ramsey Medical Center / Ramsey Clinic; Assistant Professor of Medicine, University of Minnesota Medical School, Minneapolis.
(Original Issue EM 4/18)



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***CAPOTEN® (captopril tablets) may be used as initial therapy only for patients with normal renal function in whom the risk of neutropenia/agranulocytosis is relatively low (1 out of over 8,600 in clinical trials). Use special precautions in patients with impaired renal function, collagen vascular disorders, or those exposed to other drugs known to affect the white cells or immune response. Evaluation of hypertensives should always include assessment of renal function. Overall, the most frequently occurring adverse reactions associated with CAPOTEN are skin rash and taste alteration; both effects are generally mild, reversible, or self-limited. See INDICATIONS AND USAGE, WARNINGS, and ADVERSE REACTIONS in the brief summary on the adjacent page.**

1. Croog SH, Levine S, Testa MA, et al: The effects of antihypertensive therapy on the quality of life. N Engl J Med 314(26):1657-1664, 1986.

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We spend so much of our lives at work...it's no wonder our work performance is key to our quality of life. Work performance is also a key factor in assessing antihypertensive therapy. CAPOTEN improved hypertensive patients' work performance (e.g., ability to keep pace with the job, concentration, job satisfaction, less on-the-job fatigue).[1] So, for hypertensive patients who work, why not prescribe the antihypertensive that can work for them... CAPOTEN.

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INDICATIONS: Hypertension – CAPOTEN (captopril) is indicated for the treatment of hypertension. Consideration should be given to the risk of neutropenia/agranulocytosis (see WARNINGS). CAPOTEN may be used as initial therapy for patients with normal renal function, in whom the risk is relatively low. In patients with impaired renal function, particularly those with collagen vascular disease, captopril should be reserved for those who have either developed unacceptable side effects on other drugs, or have failed to respond satisfactorily to drug combinations. CAPOTEN is effective alone and in combination with other antihypertensive agents, especially thiazide-type diuretics.

Heart Failure: CAPOTEN (captopril) is indicated in patients with heart failure who have not responded adequately to or cannot be controlled by conventional diuretic and digitalis therapy. CAPOTEN is to be used with diuretics and digitalis.

CONTRAINDICATIONS: CAPOTEN is contraindicated in patients who are hypersensitive to this product.

WARNINGS: Neutropenia/Agranulocytosis – Neutropenia (< 1000/mm³) with myeloid hypoplasia has resulted from use of captopril. About half of the neutropenic patients developed systemic or oral cavity infections or other features of the syndrome of agranulocytosis. The risk of neutropenia is dependent on the clinical status of the patient:

In clinical trials in patients with hypertension who have normal renal function (serum creatinine less than 1.6 mg/dL and no collagen vascular disease), neutropenia has been seen in one patient out of over 8,600 exposed. In patients with some degree of renal failure (serum creatinine at least 1.6 mg/dL) but no collagen vascular disease, the risk in clinical trials was about 1 per 500. Doses were relatively high in these patients, particularly in view of their diminished renal function. In patients with collagen vascular diseases (e.g., systemic lupus erythematosus, scleroderma) and impaired renal function, neutropenia occurred in 3.7% of patients in clinical trials. While none of the over 750 patients in formal clinical trials of heart failure developed neutropenia, it has occurred during the subsequent clinical experience. Of reported cases, about half had serum creatinine ≥ 1.6 mg/dL and more than 75% received procainamide. In heart failure, it appears that the same risk factors for neutropenia are present.

Neutropenia has appeared usually within 3 months after starting therapy, associated with myeloid hypoplasia and frequently accompanied by erythroid hypoplasia and decreased numbers of megakaryocytes (e.g., hypoplastic bone marrow and pancytopenia); anemia and thrombocytopenia were sometimes seen. Neutrophils generally returned to normal in about 2 weeks after captopril was discontinued, and serious infections were limited to clinically complex patients. About 13% of the cases of neutropenia have ended fatally, but almost all fatalities were in patients with serious illness, having collagen vascular disease, renal failure, heart failure or immunosuppressant therapy, or a combination of these complicating factors. **Evaluation of the hypertensive or heart failure patient should always include assessment of renal function.** If captopril is used in patients with impaired renal function, white blood cell and differential counts should be evaluated prior to starting treatment and at approximately 2-week intervals for about 3 months, then periodically. In patients with collagen vascular disease or who are exposed to other drugs known to affect the white cells or immune response, particularly when there is impaired renal function, captopril should be used only after an assessment of benefit and risk, and then with caution. All patients treated with captopril should be told to report any signs of infection (e.g., sore throat, fever). If infection is suspected, perform white cell counts without delay. Since discontinuation of captopril and other drugs has generally led to prompt return of the white count to normal, upon confirmation of neutropenia (neutrophil count < 1000/mm³) withdraw captopril and closely follow the patient's course.

Proteinuria: Total urinary proteins > 1 g per day were seen in about 0.7% of patients on captopril. About 90% of affected patients had evidence of prior renal disease or received high doses (> 150 mg/day), or both. The nephrotic syndrome occurred in about one-fifth of proteinuric patients. In most cases, proteinuria subsided or cleared within 6 months whether or not captopril was continued. The BUN and creatinine were seldom altered in proteinuric patients. Since most cases of proteinuria occurred by the 8th month of therapy with captopril, patients with prior renal disease or those receiving captopril at doses > 150 mg per day, should have urinary protein estimates (dip-stick on 1st morning urine) before therapy, and periodically thereafter.

Hypotension: Excessive hypotension was rarely seen in hypertensive patients but is a possibility in severely salt/volume-depleted persons such as those treated vigorously with diuretics (see PRECAUTIONS [Drug Interactions]). In heart failure, where the blood pressure was either normal or low, transient decreases in mean blood pressure > 20% were recorded in about half of the patients. This transient hypotension may occur after any of the first several doses and is usually well tolerated, although rarely it has been associated with arrhythmia or conduction defects. A starting dose of 6.25 or 12.5 mg tid may minimize the hypotensive effect. Patients should be followed closely for the first 2 weeks of treatment and whenever the dose of captopril and/or diuretic is increased.

BECAUSE OF THE POTENTIAL FALL IN BLOOD PRESSURE IN THESE PATIENTS, THERAPY SHOULD BE STARTED UNDER VERY CLOSE MEDICAL SUPERVISION.

PRECAUTIONS: General: *Impaired Renal Function* – Hypertension – Some hypertensive patients with renal disease, particularly those with severe renal artery stenosis, have developed increases in BUN and serum creatinine. It may be necessary to reduce captopril dosage and/or discontinue diuretic. For some of these patients, normalization of blood pressure and maintenance of adequate renal perfusion may not be possible. Heart Failure – About 20% of patients develop stable elevations of BUN and serum creatinine > 20% above normal or baseline upon long-term treatment. Less than 5% of patients, generally with severe preexisting renal disease, required discontinuation due to progressively increasing creatinine. See DOSAGE AND ADMINISTRATION, ADVERSE REACTIONS [Altered Laboratory Findings]. *Valvular Stenosis* – A theoretical concern, for risk of decreased coronary perfusion, has been noted regarding vasodilator treatment in patients with aortic stenosis due to decreased afterload reduction. *Surgery/Anesthesia* – If hypotension occurs during surgery or anesthesia, and is considered due to the effects of captopril, it is correctable by volume expansion.

Drug Interactions: *Hypotension – Patients on Diuretic Therapy* – Precipitous reduction of blood pressure may occasionally occur within the 1st hour after administration of the initial of captopril dose in patients on diuretics, especially those recently placed on diuretics, and those on severe dietary salt restriction or dialysis. This possibility can be minimized by either discontinuing the diuretic or increasing the salt intake about 1 week prior to initiation of captopril therapy or by initiating therapy with small doses (6.25 or 12.5 mg). Alternatively, provide medical supervision for at least 1 hour after the initial dose.

Agents Having Vasodilator Activity – In heart failure patients, vasodilators should be administered with caution.

Agents Causing Renin Release – Captopril's effect will be augmented by antihypertensive agents that cause renin release.

Agents Affecting Sympathetic Activity – The sympathetic nervous system may be especially important in supporting blood pressure in patients receiving captopril alone or with diuretics. Beta-adrenergic blocking drugs add some further antihypertensive effect to captopril, but the overall response is less than additive. Therefore, use agents affecting sympathetic activity (e.g., ganglionic blocking agents or adrenergic neuron blocking agents) with caution.

Agents Increasing Serum Potassium – Give potassium-sparing diuretics or potassium supplements only for documented hypokalemia, and then with caution, since they may lead to a significant increase of serum potassium. Use potassium-containing salt substitutes with caution.

Inhibitors of Endogenous Prostaglandin Synthesis – Indomethacin and other nonsteroidal anti-inflammatory agents may reduce the antihypertensive effect of captopril, especially in low renin hypertension.

Drug/Laboratory Test Interaction: Captopril may cause a false-positive urine test for acetone.

Carcinogenesis, Mutagenesis and Impairment of Fertility: Two-year studies with doses of 50 to 1350 mg/kg/day in mice and rats failed to show any evidence of carcinogenic potential. Studies in rats have revealed no impairment of fertility.

Pregnancy: Category C: There are no adequate and well-controlled studies in pregnant women. Embryocidal effects and craniofacial malformations were observed in rabbits. Therefore, captopril should be used during pregnancy, or for patients likely to become pregnant, only if the potential benefit outweighs the potential risk to the fetus. Captopril crosses the human placenta.

Nursing Mothers: Captopril is secreted in human milk. Exercise caution when administering captopril to a nursing woman, and, in general, nursing should be interrupted.

Pediatric Use: Safety and effectiveness in children have not been established although there is limited experience with use of captopril in children from 2 months to 15 years of age. Dosage, on a weight basis, was comparable to that used in adults. CAPOTEN (captopril) should be used in children only if other measures for controlling blood pressure have not been effective.

ADVERSE REACTIONS: Reported incidences are based on clinical trials involving approximately 7000 patients.

Renal – About 1 of 100 patients developed proteinuria (see WARNINGS). Renal insufficiency, renal failure, polyuria, oliguria, and urinary frequency in 1 to 2 of 1000 patients.

Hematologic – Neutropenia/agranulocytosis has occurred (see WARNINGS). Anemia, thrombocytopenia, and pancytopenia have been reported.

Dermatologic – Rash, (usually maculopapular, rarely urticarial), often with pruritus, and sometimes with fever and eosinophilia, in about 4 to 7 of 100 patients (depending on renal status and dose), usually during the 1st 4 weeks of therapy. Pruritus, without rash, in about 2 of 100 patients. A reversible associated pemphigoid-like lesion, and photosensitivity, have also been reported. Angioedema of the face, mucous membranes of the mouth, or of the extremities in about 1 of 1000 patients – reversible on discontinuance of captopril therapy. One case of laryngeal edema has been reported. Flushing or pallor in 2 to 5 of 1000 patients.

Cardiovascular – Hypotension may occur; see WARNINGS and PRECAUTIONS [Drug Interactions] for discussion of hypotension on initiation of captopril therapy. Tachycardia, chest pain, and palpitations each in about 1 of 100 patients. Angina pectoris, myocardial infarction, Raynaud's syndrome, and congestive heart failure each in 2 to 3 of 1000 patients.

Dysgeusia – Approximately 2 to 4 (depending on renal status and dose) of 100 patients developed a diminution or loss of taste perception; taste impairment is reversible and usually self-limited even with continued drug use (2 to 3 months). Gastric irritation, abdominal pain, nausea, vomiting, diarrhea, anorexia, constipation, aphthous ulcers, peptic ulcer, dizziness, headache, malaise, fatigue, insomnia, dry mouth, dyspnea, cough, alopecia, paresthesias reported in about 0.5 to 2% of patients but did not appear at increased frequency compared to placebo or other treatments used in controlled trials.

Altered Laboratory Findings: Elevations of liver enzymes in a few patients although no causal relationship has been established. Rarely cholestatic jaundice, and hepatocellular injury with or without secondary cholestasis, have been reported. A transient elevation of BUN and serum creatinine may occur, especially in volume-depleted or renovascular hypertension patients. In instances of rapid reduction of longstanding or severely elevated blood pressure, the glomerular filtration rate may decrease transiently, also resulting in transient rises in serum creatinine and BUN. Small increases in serum potassium concentration frequently occur, especially in patients with renal impairment (see PRECAUTIONS).

OVERDOSAGE: Primary concern is correction of hypotension. Volume expansion with an I.V. infusion of normal saline is the treatment of choice for restoration of blood pressure. Captopril may be removed from the general circulation by hemodialysis.

DOSAGE AND ADMINISTRATION: CAPOTEN (captopril) should be taken one hour before meals. In hypertension, CAPOTEN may be dosed bid or tid. Dosage must be individualized; see DOSAGE AND ADMINISTRATION section of package insert for detailed information regarding dosage in hypertension and in heart failure. Because CAPOTEN (captopril) is excreted primarily by the kidneys, dosage adjustments are recommended for patients with impaired renal function.

Consult package insert before prescribing CAPOTEN (captopril).

HOW SUPPLIED: Available in tablets of 12.5, 25, 50, and 100 mg in bottles of 100 (25 mg and 50 mg also available in bottles of 1000), and in UNIMATIC® unit-dose packs of 100 tablets. (J3-658J)

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Now on Medi-Cal

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Just one tablet once a day in duodenal ulcer

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Healing often complete by week 4.

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Generally well tolerated—adverse reaction incidence comparable to placebo in clinical studies.

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One 40-mg tablet h.s. for acute therapy in active duodenal ulcer.

One 20-mg tablet h.s. for maintenance therapy in duodenal ulcer.

Dosing intervals may need to be prolonged or dosage reduced in patients with severe renal insufficiency (creatinine clearance <10 mL/min).

Medi-Cal Approval Numbers

1758 F	1758 D
40-mg tablet	20-mg tablet

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TABLETS, 20 mg and 40 mg

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40 mg per 5 mL

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20 mg per 2 mL

Contraindications: Hypersensitivity to any component.

Precautions: ***General:*** Symptomatic response to therapy does not preclude the presence of gastric malignancy.

Patients with Severe Renal Insufficiency: Longer intervals between doses or lower doses may be needed in patients with severe renal insufficiency (creatinine clearance <10 mL/min) to adjust for the longer elimination half-life of famotidine (see Clinical Pharmacology and Dosage and Administration sections of Prescribing Information).

Information for Patients: The oral suspension should be shaken vigorously for 5-10 seconds prior to each use, and unused constituted oral suspension should be discarded after 30 days.

Drug Interactions: No drug interactions have been identified. Compounds tested in man include warfarin, theophylline, phenytoin, diazepam, aminopyrine, and antipyrine.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In rats and mice given oral doses up to approximately 2500 times the recommended human dose for active duodenal ulcer, there was no evidence of carcinogenic potential, no evidence of a mutagenic effect, and fertility and reproductive performance were not affected.

Pregnancy: *Pregnancy Category B*—There are no adequate or well-controlled studies in pregnant women. Use during pregnancy only if clearly needed.

Nursing Mothers: It is not known whether famotidine is secreted into human milk; however, it is secreted into the milk of lactating rats. A decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness in children have not been established.

Use in Elderly Patients: No dosage adjustment is required based on age but may be necessary in severe renal impairment (see Clinical Pharmacology section of Prescribing Information).

Adverse Reactions: The adverse reactions listed below have been reported during domestic and international clinical trials in approximately 2500 patients. In the placebo-controlled clinical trials, the incidence of adverse experiences with PEPCID Tablets, 40 mg at bedtime, was similar to that with placebo.

Incidence Greater than 1%: The following adverse reactions have been reported to occur in more than 1% of patients on therapy with PEPCID in controlled clinical trials and may be causally related to the drug: headache (4.7%), dizziness (1.3%), constipation (1.2%), and diarrhea (1.7%).

Causal Relationship Unknown: The following other adverse reactions have been reported in clinical trials. While a causal relationship could not be established for these infrequently reported events, causality cannot be excluded. *Body as a Whole*—Fever, asthenia, fatigue. *Cardiovascular*—Palpitations. *Gastrointestinal*—Nausea, vomiting, abdominal discomfort, anorexia, dry mouth, liver enzyme abnormalities. *Hematologic*—Thrombocytopenia. *Hypersensitivity*—Orbital edema, conjunctival injection. *Musculoskeletal*—Musculoskeletal pain, arthralgia. *Nervous System/Psychiatric*—Paresthesias; grand mal seizures (single report); psychic disturbances including depression, anxiety, decreased libido, hallucinations (single report); insomnia; somnolence. *Respiratory*—Bronchospasm. *Skin*—Alopecia, acne, pruritus, rash, dry skin, flushing. *Special Senses*—Tinnitus, taste disorder.

The adverse reactions reported for PEPCID Tablets may also occur with PEPCID Oral Suspension or PEPCID I.V.; in addition, transient irritation at the injection site has been observed with PEPCID I.V.

Management of Overdosage: There is no experience to date with deliberate overdosage. Up to 640 mg/day have been given to patients with pathological hypersecretory conditions with no serious adverse effects. In the event of overdosage, treatment should be symptomatic and supportive. Unabsorbed material should be removed from the gastrointestinal tract, the patient should be monitored, and supportive therapy should be employed.

Dosage and Administration: ***Duodenal Ulcer:*** The recommended adult oral dosage for active duodenal ulcer is 40 mg h.s.; most patients heal within 4 weeks, and it is rarely necessary to use the full dosage for longer than 6 to 8 weeks. A regimen of 20 mg b.i.d. is also effective. For maintenance therapy, the recommended oral dosage is 20 mg h.s.

Pathological Hypersecretory Conditions (e.g., Zollinger-Ellison Syndrome, Multiple Endocrine Adenomas): The dosage varies with the individual patient; the recommended adult oral starting dosage is 20 mg q6h, but some patients may require a higher starting dosage. Dosages should be adjusted to individual patient needs and continued as long as clinically indicated; up to 160 mg q6h have been administered to some patients with severe Zollinger-Ellison syndrome.

Oral Suspension: The Oral Suspension may be substituted for Tablets for those patients who cannot swallow tablets.

Directions for Preparing PEPCID Oral Suspension: Prepare suspension at time of dispensing. Slowly add 46 mL Purified Water. Shake vigorously for 5-10 seconds immediately after adding the water and immediately before use.

Stability of PEPCID Oral Suspension: Unused constituted oral suspension should be discarded after 30 days.

Intravenous Administration: In some hospitalized patients with pathological hypersecretory conditions or intractable ulcers, or in patients who are unable to take oral medication, the recommended intravenous dosage is 20 mg q12h. For preparation of solutions for injection or infusion and for compatible diluents, please see Prescribing Information. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

Concomitant Use of Antacids: Antacids may be given concomitantly if needed.

Dosage Adjustment for Patients with Severe Renal Insufficiency: In patients with severe renal insufficiency (creatinine clearance less than 10 mL/min), the elimination half-life of famotidine may exceed 20 hours, reaching approximately 24 hours in anuric patients. Although no relationship of adverse effects to high plasma levels has been established, to avoid excess accumulation of the drug, the dosage may be reduced to 20 mg h.s. or the dosing interval may be prolonged to 36 to 48 hours as indicated by the patient's clinical response.

How Supplied: Tablets, containing 20 mg or 40 mg famotidine, with hydroxypropyl cellulose, hydroxypropyl methylcellulose, iron oxides, magnesium stearate, microcrystalline cellulose, starch, talc, and titanium dioxide as inactive ingredients, in bottles of 30 and unit-dose packages of 100; Oral Suspension, containing per 5 mL after constitution with 46 mL Purified Water, 40 mg famotidine, with citric acid, flavors, microcrystalline cellulose and carboxymethylcellulose sodium, sucrose, and xanthan gum as inactive ingredients, and sodium benzoate 0.1%, sodium methylparaben 0.1%, and sodium propylparaben 0.02% added as preservatives, in bottles of 400 mg famotidine for constitution; Solution for intravenous injection, containing 10 mg famotidine per mL, with L-aspartic acid 4 mg, mannitol 20 mg, and water for injection q.s. 1 mL as inactive ingredients, and benzyl alcohol 0.9% added as preservative to the multidose vial, as 10x2-mL single-dose vials and as 4-mL vials.

For more detailed information, consult your MSD Representative or see Prescribing Information.
Merck Sharp & Dohme, Division of Merck & Co., Inc., West Point, PA 19486

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The Western Journal of Medicine

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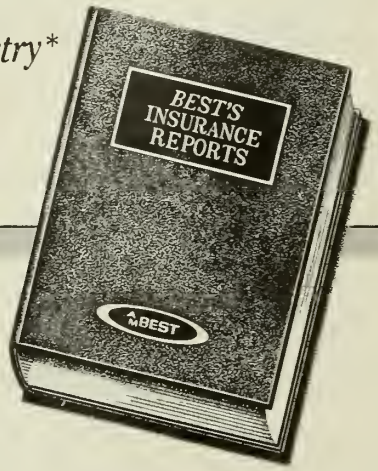

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r Brief Summary, please see last page of this advertisement.

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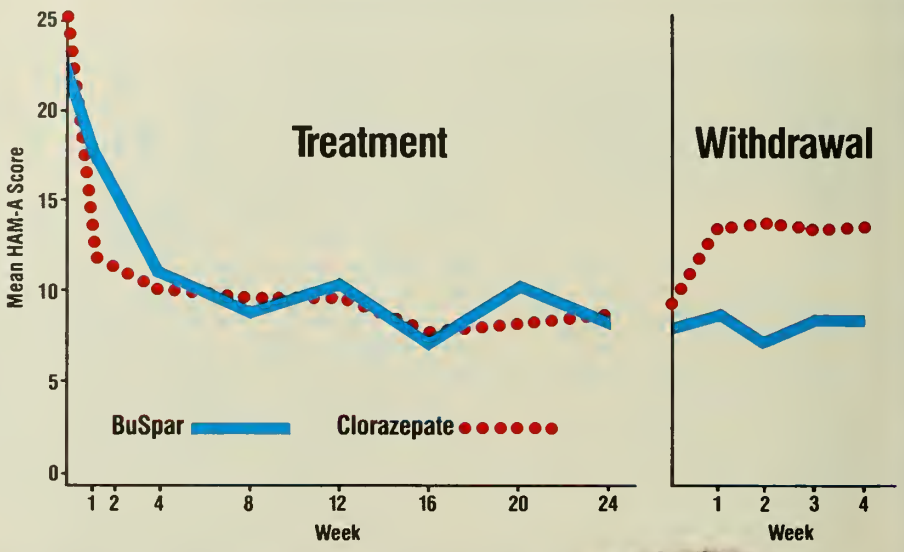

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The first choice for chronic anxiety

BuSpar effectively relieves the symptoms of anxiety—such as irritability, inability to concentrate, and excessive worry or fearfulness—generally without producing euphoria[2] and with no more drowsiness (10%) than induced by placebo (9%).[3]

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No withdrawal syndrome has been demonstrated in clinical trials with BuSpar, even on abrupt discontinuation of therapy.[1] As a result, you stay in control of the treatment you prescribed.

Counseling and follow-up are important. Patients should be advised that BuSpar does not produce a tranquilizer "buzz," but instead will relieve their symptoms gradually and steadily. Improvement generally is noted within 7 to 10 days. Patients should be monitored for relief of symptoms, improvement in functioning, and an increased capacity to cope.

BuSpar is not a controlled substance. Side effects associated with the use of BuSpar not seen at an equivalent incidence among placebo-treated patients in controlled clinical trials were dizziness (12%), nausea (8%), headache (6%), nervousness (5%), lightheadedness (3%), and excitement (2%).

*Study conducted in normal volunteers. Patients should be cautioned about operating an automobile or using complex machinery until they are reasonably certain that BuSpar treatment does not affect them adversely.

**While formal studies of the interaction of BuSpar with alcohol indicate that it does not increase alcohol-induced impairment in motor and mental performance, it is prudent to avoid concomitant use of alcohol and BuSpar.

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A different kind of calm

For Brief Summary, please see following page.

BuSpar® (buspirone HCl)

References: 1. Lader M. Assessing the potential for buspirone dependence or abuse and effects of its withdrawal. *Am J Med* 1987;82(suppl 5A):20-26. **2.** Cole JO, *et al.* Assessment of the abuse liability of buspirone in recreational sedative users. *J Clin Psychiatry* 1982;43(12,Sec 2):69-74. **3.** Newton RE, *et al.* A review of the side effect profile of buspirone. *Am J Med* 1986;80(suppl 3B):17-21. **4.** Lucki I, *et al.* Differential effects of the anxiolytic drugs, diazepam and buspirone, on memory function. *Br J Clin Pharmacol* 1987;23:207-211. **5.** Moskowitz H and Smiley A. Effects of chronically administered buspirone and diazepam on driving-related skills performance. *J Clin Psychiatry* 1982;43(12,Sec 2):45-55. **6.** Mallia MJ, *et al.* Acute effects of buspirone and alcohol on psychomotor skills. *J Clin Psychiatry* 1982;43(12,Sec 2):56-60.

Contraindications: Hypersensitivity to buspirone

Warnings: The administration of BuSpar to a patient taking a monoamine oxidase inhibitor (MAOI) may pose a hazard. Since blood pressure has become elevated when BuSpar was administered concomitantly with an MAOI, such concomitant use is not recommended. BuSpar should not be employed in lieu of appropriate antipsychotic treatment.

Precautions: ***General***—*Interference with cognitive and motor performance:* Although buspirone is less sedating than other anxiolytics and does not produce significant functional impairment, its CNS effects in a given patient may not be predictable; therefore, patients should be cautioned about operating an automobile or using complex machinery until they are reasonably certain that buspirone does not affect them adversely. Although buspirone has not been shown to increase alcohol-induced impairment in motor and mental performance, it is prudent to avoid concomitant use with alcohol.

Potential for withdrawal reactions in sedative/hypnotic/anxiolytic drug dependent patients: Because buspirone will not block the withdrawal syndrome often seen with cessation of therapy with benzodiazepines and other common sedative/hypnotic drugs, before starting buspirone withdraw patients gradually from their prior treatment, especially those who used a CNS depressant chronically. Rebound or withdrawal symptoms may occur over varying time periods, depending in part on the type of drug and its elimination half-life. The withdrawal syndrome can appear as any combination of irritability, anxiety, agitation, insomnia, tremor, abdominal cramps, muscle cramps, vomiting, sweating, flu-like symptoms without fever, and occasionally, even as seizures.

Possible concerns related to buspirone's binding to dopamine receptors: Because buspirone can bind to central dopamine receptors, a question has been raised about its potential to cause acute and chronic changes in dopamine mediated neurological function (e.g., dystonia, pseudoparkinsonism, akathisia, and tardive dyskinesia). Clinical experience in controlled trials has failed to identify any significant neuroleptic-like activity; however, a syndrome of restlessness, appearing shortly after initiation of treatment, has been reported, the syndrome may be due to increased central noradrenergic activity or may be attributable to dopaminergic effects (i.e., represent akathisia).

Information for Patients—Patients should be instructed to inform their physician about any medications, prescription or non-prescription, alcohol or drugs they are now taking or plan to take during treatment with buspirone, to inform their physician if they are pregnant, are planning to become pregnant, or become pregnant while taking buspirone; to inform their physician if they are breast feeding; and not to drive a car or operate potentially dangerous machinery until they experience how this medication affects them.

Drug Interactions—Concomitant use with other CNS active drugs should be approached with caution (see **Warnings**). Concomitant use with trazodone may have caused 3- to 6-fold elevations on SGPT (ALT) in a few patients. Buspirone does not displace tightly bound drugs like phenytoin, propranolol, and warfarin from serum proteins, but may displace less firmly bound drugs like digoxin.

Carcinogenesis, Mutagenesis, Impairment of Fertility—No evidence of carcinogenic potential was observed in rats or mice; buspirone did not induce point mutations, nor was DNA damage observed; chromosomal aberrations or abnormalities did not occur.

Pregnancy: Teratogenic Effects—Pregnancy Category B: Should be used during pregnancy only if clearly needed.

Nursing Mothers—Administration to nursing women should be avoided if clinically possible.

Pediatric Use—The safety and effectiveness have not been determined in individuals below 18 years of age.

Use in the Elderly—No unusual, adverse, age-related phenomena have been identified in elderly patients receiving a total, modal daily dose of 15 mg.

Use in Patients with Impaired Hepatic or Renal Function—Since buspirone is metabolized by the liver and excreted by the kidneys, it is not recommended in severe hepatic or renal impairment.

Adverse Reactions (See also Precautions): ***Commonly Observed***—The more commonly observed untoward events include dizziness, nausea, headache, nervousness, lightheadedness, and excitement.

Associated with Discontinuation of Treatment—The more common events causing discontinuation included: central nervous system disturbances (3.4%), primarily dizziness, insomnia, nervousness, drowsiness, lightheaded feeling, gastrointestinal disturbances (1.2%), primarily nausea; miscellaneous disturbances (1.1%), primarily headache and fatigue. In addition, 3.4% of patients had multiple complaints, none of which could be characterized as primary.

Incidence in Controlled Clinical Trials—Adverse events reported by 1% or more of 477 patients who received buspirone in four-week, controlled trials: *Cardiovascular:* Tachycardia/palpitations 1%. *CNS:* Dizziness 12%, drowsiness 10%, nervousness 5%, insomnia 3%, lightheadedness 3%, decreased concentration 2%, excitement 2%, anger/hostility 2%, confusion 2%, depression 2%. *EENT:* Blurred vision 2%. *Gastrointestinal:* Nausea 8%, dry mouth 3%, abdominal/gastric distress 2%, diarrhea 2%, constipation 1%, vomiting 1%. *Musculoskeletal:* Musculoskeletal aches/pains 1%. *Neurological:* Numbness 2%, paresthesia 1%, incoordination 1%, tremor 1%. *Skin:* Skin rash 1%. *Miscellaneous:* Headache 6%, fatigue 4%, weakness 2%, sweating/clamminess 1%.

Other Events Observed During the Entire Pre-marketing Evaluation—The relative frequency of all other undesirable events reasonably associated with the use of buspirone in approximately 3000 subjects who took multiple doses of the drug under well-controlled, open, and uncontrolled conditions is defined as follows: Frequent are those occurring in at least 1/100 patients; infrequent are those occurring in 1/100 to 1/1000 patients; and rare are those occurring in less than 1/1000 patients. *Cardiovascular*—frequent: nonspecific chest pain; infrequent: syncope, hypotension, hypertension; rare: cerebrovascular accident, congestive heart failure, myocardial infarction, cardiomyopathy, bradycardia. *Central Nervous System*—frequent: dream disturbances; infrequent: depersonalization, dysphoria, noise intolerance, euphoria, akathisia, tearfulness, loss of interest, dissociative reaction, hallucinations, suicidal ideation, seizures; rare: feelings of claustrophobia, cold intolerance, stupor, slurred speech, psychosis. *EENT*—frequent: tinnitus, sore throat, nasal congestion; infrequent: redness and itching of the eyes, altered taste, altered smell, conjunctivitis; rare: inner ear abnormality, eye pain, photophobia, pressure on eyes. *Endocrine*—rare: galactorrhea, thyroid abnormality. *Gastrointestinal*—infrequent: flatulence, anorexia, increased appetite, salivation, irritable colon, rectal bleeding; rare: burning of the tongue. *Genitourinary*—infrequent: urinary frequency, urinary hesitancy, menstrual irregularity and spotting, dysuria; rare: amenorrhea, pelvic inflammatory disease, enuresis, nocturia. *Musculoskeletal*—infrequent: muscle cramps, muscle spasms, rigid/stiff muscles, arthralgias. *Neurological*—infrequent: involuntary movements, slowed reaction time; rare: muscle weakness. *Respiratory*—infrequent: hyperventilation, shortness of breath, chest congestion; rare: epistaxis. *Sexual Function*—infrequent: decreased or increased libido; rare: delayed ejaculation, impotence. *Skin*—infrequent: edema, pruritus, flushing, easy bruising, hair loss, dry skin, facial edema, blisters; rare: acne, thinning of nails. *Clinical Laboratory*—infrequent: increases in hepatic aminotransferases (SGOT, SGPT); rare: eosinophilia, leukopenia, thrombocytopenia. *Miscellaneous*—infrequent: weight gain, fever, roaring sensation in the head, weight loss, malaise; rare: alcohol abuse, bleeding disturbance, loss of voice, hiccoughs.

Drug Abuse and Dependence: ***Controlled Substance Class***—Not a controlled substance.

Physical and Psychological Dependence—Buspirone has shown no potential for abuse or diversion and there is no evidence that it causes tolerance, or either physical or psychological dependence. However, since it is difficult to predict from experiments the extent to which a CNS active drug will be misused, diverted, and/or abused once marketed, physicians should carefully evaluate patients for a history of drug abuse and follow such patients closely, observing them for signs of buspirone misuse or abuse (e.g., development of tolerance, incrementation of dose, drug-seeking behavior).

Overdosage: ***Signs and Symptoms***—At doses approaching 375 mg/day the following symptoms were observed: nausea, vomiting, dizziness, drowsiness, miosis, and gastric distress. No deaths have been reported in humans either with deliberate or accidental overdosage.

Recommended Overdose Treatment—General symptomatic and supportive measures should be used along with immediate gastric lavage. No specific antidote is known and dialyzability of buspirone has not been determined.

For complete details, see Prescribing Information or consult your Mead Johnson Pharmaceuticals Representative.

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ARIZONA

The following list of continuing medical education programs in Arizona is compiled by the Arizona Medical Association. All courses listed have been certified as meeting the criteria for Category I of the ArMA CME Certificate and the AMA Physicians Recognition Award. To list Category I continuing medical education programs, please send information to Arizona Medical Association, 810 West Bethany Home Road, Phoenix, AZ 85013; or phone (602) 246-8901.

Brochures and registration forms are available from the contact person or organization sponsoring the program.

June 9—**Arizona Medical Association Annual Scientific Session.** Loews Ventana Canyon Resort, Tucson. Thurs. Contact: ArMA.

PATHOLOGY

May 14-15—**Selected Topics in Gynecologic Pathology.** Arizona Society of Pathologists and U of A at Westward Look Resort, Tucson. Sat-Sun. 7 hrs. Contact: Beverly Richter, Arizona Society of Pathologists, 810 W Bethany Home Rd, Phoenix 85013. (602) 246-8901.

CONTACT INFORMATION

ArMA—Contact: Arizona Medical Association, 810 W Bethany Home Rd, Phoenix, AZ 85013. (602) 246-8901.

U of A—Contact: University of Arizona College of Medicine, Arizona Health Sciences Center, Tucson, AZ 85724. (602) 626-6707.

CALIFORNIA, HAWAII AND NEVADA

This listing of continuing education programs in California, Hawaii and Nevada is supplied by the Committee on Continuing Medical Education of the California Medical Association. All courses and meetings listed have been approved for Category I credit toward the CMA Certificate in Continuing Medical Education. To have accredited courses listed here, please send information at least two months in advance to Department of Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690; or phone (415) 863-5522. For a list of organizations approved for Category I credit toward the CMA Certificate in Continuing Medical Education or for more information on accreditation or certification, please write to the above address.

ANESTHESIOLOGY

May 15-20—**Hawaiian Seminar on Clinical Anesthesia.** California Society of Anesthesiologists at Sheraton Kauai Hotel, Poipu Beach, Kauai. Sun-Fri. 20 hrs. $325-375. Contact: California Society of Anesthesiologists, 1065 Hillsdale Blvd, #410, Foster City 94404. (415) 345-3020.

May 16-20—**5th International Symposium: Computing in Anesthesia and Intensive Care.** UCSD at US Grant Hotel, San Diego. Mon-Fri. 20 hrs. $300. Contact: UCSD.

June 16-19—**California Society of Anesthesiologists 1988 Annual Meeting** at Marriott Hotel, Anaheim. Thurs-Sun. 16 hrs. $150-225. Contact: California Society of Anesthesiologists, 1065 Hillsdale Blvd, #410, Foster City 94404. (415) 345-3020.

August 21-27—**Hawaiian Seminar on Clinical Anesthesia.** California Society of Anesthesiologists at Inter-Continental Hotel, Wailea, Maui. Sun-Sat. 20 hrs. $325/$375. Contact: CSA, 1065 E. Hilldale Blvd, Suite 410, Foster City 94404. (415) 345-3020.

September 30-October 1—**Anesthesia Practice 1988.** Anesthesiology Educational Foundation. Fri-Sun. 11 hrs. Contact: AEF, PO Box 24230, Federal Building, Los Angeles 90024. (213) 825-0736.

October 16-21—**Hawaiian Seminar on Clinical Anesthesia.** California Society of Anesthesiologists at Westin Maui Hotel, Maui. Sun-Fri. 20 hrs. $325/$375. Contact: CSA, 1065 Hilldale Blvd, Suite 410, Foster City 94404. (415) 345-3020.

CARDIOLOGY

May 19-20—**Cardiology for the Non-Cardiologist.** UCI. Thurs-Fri. Contact: UCI.

June 6-8—**Advanced Echocardiography & Doppler Ultrasound 1988.** American College of Cardiology at Sheraton Harbor Island, San Diego. Mon-Wed. Contact: Registration Secretary, EP Dept. ACC, 9111 Old Georgetown Road, Bethesda, MD 20814.

June 24-25—**Cardiovascular Drug Therapy II.** USC at Century Plaza Hotel, Century City. Fri-Sat. 12 hrs. $110. Contact: USC.

June 30-July 2—**Consultative Cardiology: Update in Diagnostic and Therapeutic Techniques.** ACC, Orange Coast Heart Institute and Hoag Memorial Hospital at Westin South Coast Plaza, Costa Mesa. Thur-Sat. Contact: Registration Secretary, EP Dept., ACC, 9111 Old Georgetown Road, Bethesda, MD 20814.

KEY TO ABBREVIATIONS

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690. (415) 863-5522.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Herbert M. Thomas, MD, MPH, Director of CME, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th Street, Los Angeles 90059. (213) 603-3183.

LLU: Loma Linda University
Contact: Varner J. Johns, Jr, MD, Associate Dean for Continuing Medical Education, Loma Linda University School of Medicine, Loma Linda 92354. (714) 796-7311, ext 2400.

PMC: Pacific Medical Center
Contact: Continuing Education, Pacific Medical Center, PO Box 7999, San Francisco 94120. (415) 563-4321, ext 2761.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Medical School Office Building, Suite X-365, Stanford 94305-6114. (415) 723-5594.

UCD: University of California, Davis
Contact: Ruth Feryok, Director, Office of Continuing Medical Education, University of California, Davis, School of Medicine, 2701 Stockton Boulevard, Sacramento 95817. (916) 453-5390.

UCI: University of California, Irvine
Contact: Melvin I. Marks, MD, Assistant Dean, University of California, Irvine, California College of Medicine, c/o UCI/CME Program, Memorial Medical Center, 2801 Atlantic Avenue, Long Beach 90801-1428. (213) 595-3811, or (714) 856-5414, UCI Extension.

UCLA: University of California, Los Angeles
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, PO Box 24902, UCLA, Los Angeles 90024. (213) 825-7241.

UCSD: University of California, San Diego
Contact: Office of Continuing Medical Education, University of California, San Diego, School of Medicine (M-017), La Jolla 92093. (619) 534-3713.

UCSF: University of California, San Francisco
Contact: Robert Maggio, Administrative Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 476-4251.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 1975 Zonal Ave, KAM314, Los Angeles 90033. (213) 224-7051.

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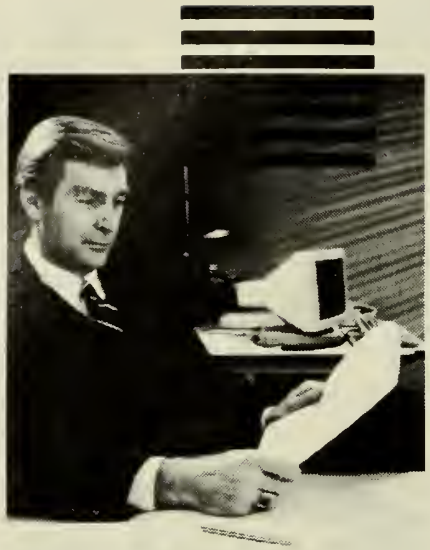

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CONTINUING MEDICAL EDUCATION

(Continued from Page 529)

July 22-23—**Arrhythmias: Interpretation, Diagnosis and Management.** Medical Education Resources at Disneyland Hotel, Anaheim. Fri-Sat. $295. Contact: Deborah Wilderson, MER, 5808 S. Rapp St, Ste 202, Littleton, CO 80120. (800) 421-3756.

October 21-22—**Arrhythmias: Interpretation, Diagnosis and Management.** Medical Education Resources at Hyatt on Union Square, San Francisco. Fri-Sat. $295. Contact: Deborah Wilderson, MER, 5808 S. Rapp St, Ste 202, Littleton, CO 80120. (800) 421-3756.

DERMATOLOGY

May 21—**Summary of Clinical Use of Argon, YAG, and CO2 Lasers for Cutaneous Lesions.** Palo Alto Medical Foundation at Palo Alto Medical Clinic. Sat. 6 hrs. Contact: Palo Alto Medical Clinic, 300 Homer Ave, Palo Alto 94301. (415) 321-4121.

August 12-14—**Dermatologic Surgery: State of the Art 1988.** Stanford University at Monterey Sheraton, Monterey. Fri-Sun. Contact: Paul H. Jacobs, MD, Dept. of Dermatology, UMC Stanford, 94305. (415) 723-6105.

August 21-28—**International Symposium: Hot Spots in Dermatology.** Kauai Medical Group at Molokai, Hawaii. One week. Contact: David Elpern, MD, 3420-B Kuhio Highway, Lihue, Hawaii 96766. (808) 245-1507.

EMERGENCY MEDICINE

June 6-10—**Topics in Emergency Medicine.** UCSF at Holiday Inn, Union Square, San Francisco. Mon-Fri. 32 hrs. $420. Contact: UCSF.

July 22-24—**Advanced Cardiac Life Support.** CPR Seminars at Ralph K. Davies Medical Center, San Francisco. Fri-Sun. Contact: CPR Seminars, 833 Market St, Ste 421, San Francisco 94103. (415) 543-7282.

August 29-September 2—**Topics in Emergency Medicine.** UCSF at Holiday Inn Union Square, San Francisco. Mon-Fri. 31 hrs. $420. Contact: UCSF.

October 21-23—**Advanced Cardiac Life Support.** CPR Seminars at Ralph K. Davies Medical Center, San Francisco. Fri-Sun. Contact: CPR Seminars, 833 Market St, Ste 421, San Francisco 94103. (415) 543-7282.

INTERNAL MEDICINE

May 23-27—**Advances in Internal Medicine.** UCSF at Sheraton-Palace Hotel, San Francisco. Mon-Fri. 32 hrs. $440. Contact: UCSF.

May 27-29—**California Society of Internal Medicine Annual Meeting** at Nikko Hotel, San Francisco. Fri-Sun. Contact: Kathy Matikonis, California Society of Internal Medicine, PO Box 880606, San Francisco, 94188-0606. (415) 882-5198.

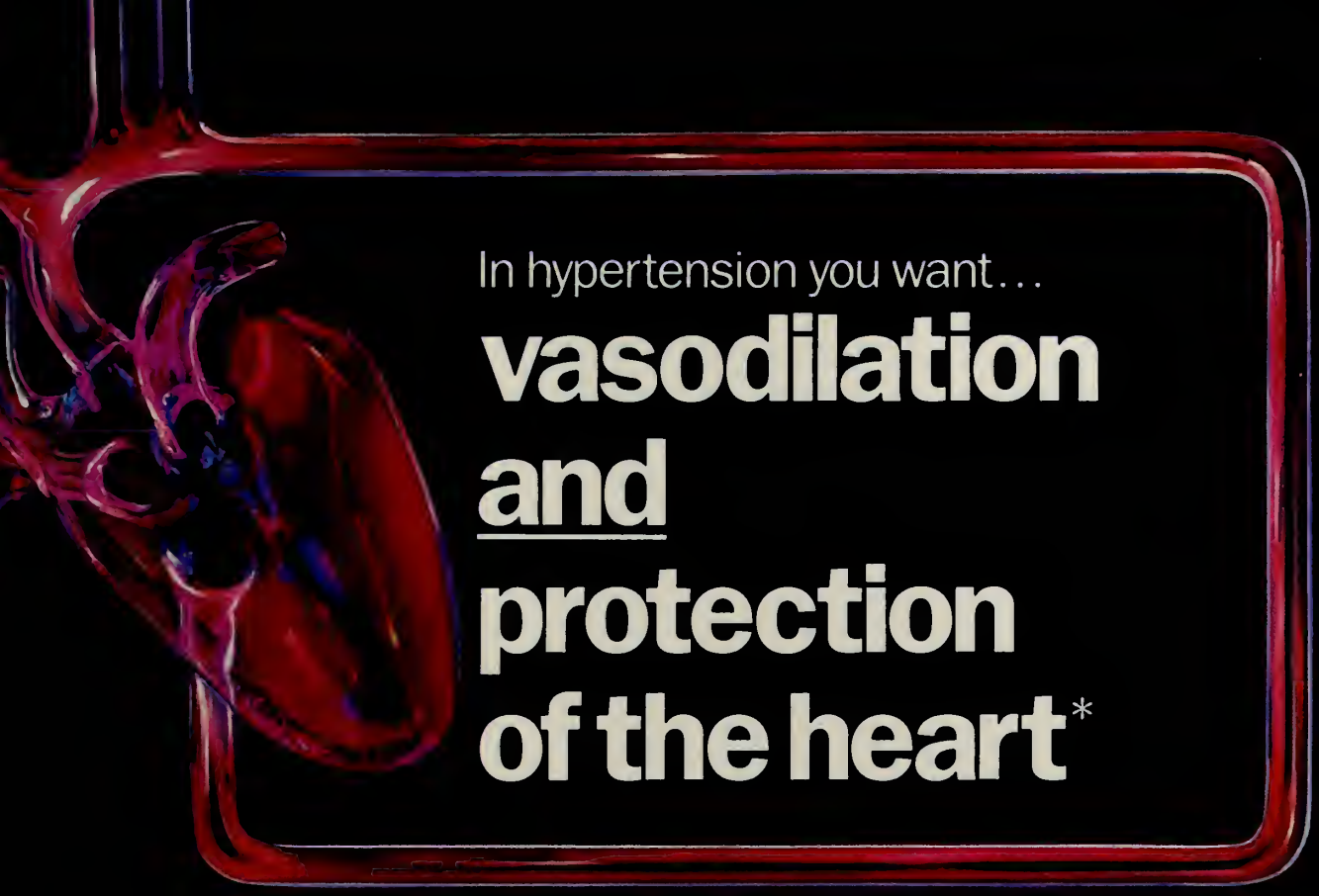
June 6-10—**Advances in Internal Medicine.** UCSF at Cole Hall. 32 hrs. $440. Contact: UCSF.

June 15-17—**Gastroenterology: Advances in Diagnosis and Management.** UCSF at The Mark Hopkins Hotel, San Francisco. Wed-Fri. 17 hrs. $375. Contact: UCSF.

June 20-24—**Advances in Internal Medicine.** UCSF at San Francisco. Mon-Fri. 32 hrs. $485. Contact: UCSF.

September 22-24—**International Symposium on Medical Virology.** UCI at Ramada Renaissance Hotel, San Francisco. Thurs-Sat. Contact: Dr Luis M. de la Maza, Department of Pathology, Rt 84, UCI Medical Center, 101 City Drive S., Orange, 92668. (714) 634-6868.

(Continued on Page 538)



NORMODYNE® (labetalol HCl) Tablets gives you both

	vasodilation	beta blockade
NORMODYNE (labetalol HCl) Tablets	✓	✓
Beta Blockers		✓
ACE Inhibitors	✓	
Calcium Channel Blockers	✓	

- ☐ Low incidence of impotence, fatigue, or cold extremities†
- ☐ Lipid and potassium levels are not adversely affected
- ☐ Minimizes risk of reflex tachycardia
- ☐ Maintains cardiac output
- ☐ Maintains exercise capacity
- ☐ Does not adversely affect heart rate
- ☐ Maintains blood flow to vital organs
- ☐ Renal function is unimpaired

*reduces double product (HR × SBP) and minimizes the risk of reflex tachycardia

Most adverse effects are mild, transient, and occur early in the course of treatment. In controlled clinical trials of three to four months' duration, the most common side effects noted in treating mild to moderate hypertension with NORMODYNE (labetalol HCl) Tablets include dizziness (11%), nausea (6%), and fatigue (5%). Dyspepsia (3%), nasal stuffiness (3%), impotence (1%), and drowsiness (<1%) occurred to a lesser degree. Overall, reports of symptomatic postural hypotension have been uncommon and have included rare instances of syncope. For complete side effects profile, see Prescribing Information.

For Brief Summary, please see reverse side of page.

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PRODUCT INFORMATION

NORMODYNE®

brand of labetalol hydrochloride

Tablets

BRIEF SUMMARY

INDICATIONS AND USAGE

NORMODYNE (labetalol HCl) Tablets are indicated in the management of hypertension. NORMODYNE Tablets may be used alone or in combination with other antihypertensive agents, especially thiazide and loop diuretics.

CONTRAINDICATIONS

NORMODYNE (labetalol HCl) Tablets are contraindicated in bronchial asthma, overt cardiac failure, greater than first degree heart block, cardiogenic shock, and severe bradycardia (see WARNINGS).

WARNINGS

Cardiac Failure Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure. Beta blockade carries a potential hazard of further depressing myocardial contractility and precipitating more severe failure. Although beta-blockers should be avoided in overt congestive heart failure, if necessary, labetalol HCl can be used with caution in patients with a history of heart failure who are well-compensated. Congestive heart failure has been observed in patients receiving labetalol HCl. Labetalol HCl does not abolish the inotropic action of digitalis on heart muscle.

In Patients Without a History of Cardiac Failure In patients with latent cardiac insufficiency, continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or be given a diuretic, and the response observed closely. If cardiac failure continues, despite adequate digitalization and diuretic, NORMODYNE (labetalol HCl) therapy should be withdrawn (gradually if possible).

Exacerbation of Ischemic Heart Disease Following Abrupt Withdrawal Angina pectoris has not been reported upon labetalol HCl discontinuation. However, hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy; exacerbation of angina and, in some cases, myocardial infarction have occurred after *abrupt* discontinuation of such therapy. When discontinuing chronically administered NORMODYNE (labetalol HCl), particularly in patients with ischemic heart disease, the dosage should be gradually reduced over a period of one to two weeks and the patient should be carefully monitored. If angina markedly worsens or acute coronary insufficiency develops, NORMODYNE (labetalol HCl) administration should be reinstituted promptly, at least temporarily, and other measures appropriate for the management of unstable angina should be taken. Patients should be warned against interruption or discontinuation of therapy without the physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue NORMODYNE (labetalol HCl) therapy abruptly even in patients treated only for hypertension.

Nonallergic Bronchospasm (e.g., chronic bronchitis and emphysema) Patients with bronchospastic disease should, in general, not receive beta-blockers. NORMODYNE may be used with caution, however, in patients who do not respond to, or cannot tolerate, other antihypertensive agents. It is prudent, if NORMODYNE is used, to use the smallest effective dose, so that inhibition of endogenous or exogenous beta-agonists is minimized.

Pheochromocytoma Labetalol HCl has been shown to be effective in lowering the blood pressure and relieving symptoms in patients with pheochromocytoma. However, paradoxical hypertensive responses have been reported in a few patients with this tumor; therefore, use caution when administering labetalol HCl to patients with pheochromocytoma.

Diabetes Mellitus and Hypoglycemia Beta-adrenergic blockade may prevent the appearance of premonitory signs and symptoms (e.g., tachycardia) of acute hypoglycemia. This is especially important with labile diabetics. Beta-blockade also reduces the release of insulin in response to hyperglycemia; it may therefore be necessary to adjust the dose of antidiabetic drugs.

Major Surgery The necessity or desirability of withdrawing beta-blocking therapy prior to major surgery is controversial. Protracted severe hypotension and difficulty in restarting or maintaining a heart beat have been reported with beta-blockers. The effect of labetalol HCl's alpha-adrenergic activity has not been evaluated in this setting.

A synergism between labetalol HCl and halothane anesthesia has been shown (see **Drug Interactions**).

PRECAUTIONS

General *Impaired Hepatic Function* NORMODYNE (labetalol HCl) Tablets should be used with caution in patients with impaired hepatic function since metabolism of the drug may be diminished.

Jaundice or Hepatic Dysfunction On rare occasions, labetalol HCl has been associated with jaundice (both hepatic and cholestatic). It is therefore recommended that treatment with labetalol HCl be stopped immediately should a patient develop jaundice or laboratory evidence of liver injury. Both have been shown to be reversible on stopping therapy.

Information for Patients

As with all drugs with beta-blocking activity, certain advice to patients being treated with labetalol HCl is warranted. This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects. While no incident of the abrupt withdrawal phenomenon (exacerbation of angina pectoris) has been reported with labetalol HCl, dosing with NORMODYNE Tablets should not be interrupted or discontinued without a physician's advice. Patients being treated with NORMODYNE Tablets should consult a physician at any sign of impending cardiac failure. Also, transient scalp tingling may occur, usually when treatment with NORMODYNE Tablets is initiated (see **ADVERSE REACTIONS**).

Laboratory Tests

As with any new drug given over prolonged periods, laboratory parameters should be observed over regular intervals. In patients with concomitant illnesses, such as impaired renal function, appropriate tests should be done to monitor these conditions.

Drug Interactions

In one survey, 2.3% of patients taking labetalol HCl in combination with tricyclic antidepressants experienced tremor as compared to 0.7% reported to occur with labetalol HCl alone. The contribution of each of the treatments to this adverse reaction is unknown but the possibility of a drug interaction cannot be excluded.

Drugs possessing beta-blocking properties can blunt the bronchodilator effect of beta-receptor agonist drugs in patients with bronchospasm; therefore, doses greater than the normal anti-asthmatic dose of beta-agonist bronchodilator drugs may be required.

Cimetidine has been shown to increase the bioavailability of labetalol HCl. Since this could be explained either by enhanced absorption or by an alteration of hepatic metabolism of labetalol HCl, special care should be used in establishing the dose required for blood pressure control in such patients.

Synergism has been shown between halothane anesthesia and intravenously administered labetalol HCl. During controlled hypotensive anesthesia using labetalol HCl in association with halothane, high concentrations (3% or above) of halothane should not be used because the degree of hypotension will be increased and because of the possibility of a large reduction in cardiac output and an increase in central venous pressure. The anesthesiologist should be informed when a patient is receiving labetalol HCl.

Labetalol HCl blunts the reflex tachycardia produced by nitroglycerin without preventing its hypotensive effect. If labetalol HCl is used with nitroglycerin in patients with angina pectoris, additional antihypertensive effects may occur.

Drug/Laboratory Test Interactions

The presence of a metabolite of labetalol in the urine may result in falsely increased levels of urinary catecholamines when measured by a nonspecific trihydroxyindole (THI) reaction. In screening patients suspected of having a pheochromocytoma and being treated with labetalol HCl, specific radioenzymatic or high performance liquid chromatography assay techniques should be used to determine levels of catecholamines or their metabolites.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term oral dosing studies with labetalol HCl for 18 months in mice and for 2 years in rats showed no evidence of carcinogenesis. Studies with labetalol HCl, using dominant lethal assays in rats and mice, and exposing microorganisms according to modified Ames tests, showed no evidence of mutagenesis.

Pregnancy Category C

Teratogenic studies have been performed with labetalol in rats and rabbits at oral doses up to approximately 6 and 4 times the maximum recommended human dose (MRHD), respectively. No reproducible evidence of fetal malformations was observed. Increased fetal resorptions were seen in both species at doses approximating the MRHD. There are no adequate and well-controlled studies in pregnant women. Labetalol should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects

Infants of mothers who were treated with labetalol HCl for hypertension during pregnancy did not appear to be adversely affected by the drug. Oral administration of labetalol to rats during late gestation through weaning at doses of 2 to 4 times the MRHD caused a decrease in neonatal survival.

Labor and Delivery

Labetalol HCl given to pregnant women with hypertension did not appear to affect the usual course of labor and delivery.

Nursing Mothers

Small amounts of labetalol (approximately 0.004% of the maternal dose) are excreted in human milk. Caution should be exercised when NORMODYNE Tablets are administered to a nursing woman.

Pediatric Use

Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Most adverse effects are mild, transient and occur early in the course of treatment. In controlled clinical trials of 3 to 4 months duration, discontinuation of NORMODYNE (labetalol HCl) Tablets due to one or more adverse effects was required in 7% of all patients. In these same trials, beta-blocker control agents led to discontinuation in 8 to 10% of patients, and a centrally acting alpha-agonist in 30% of patients.

The incidence rates of adverse reactions listed in the following table were derived from multicenter controlled clinical trials, comparing labetalol HCl, placebo, metoprolol and propranolol, over treatment periods of 3 and 4 months. Where the frequency of adverse effects for labetalol HCl and placebo is similar, causal relationship is uncertain. The rates are based on adverse reactions considered probably drug-related by the investigator. If all reports are considered, the rates are somewhat higher (e.g., dizziness 20%, nausea 14%, fatigue 11%), but the overall conclusions are unchanged.

	Labetalol HCl (N = 227) %	Placebo (N = 98) %	Propranolol (N = 84) %	Metoprolol (N = 49) %
Body as a whole				
fatigue	5	0	12	12
asthenia	1	1	1	0
headache	2	1	1	2
Gastrointestinal				
nausea	6	1	1	2
vomiting	<1	0	0	0
dyspepsia	3	1	1	0
abdominal pain	0	0	1	2
diarrhea	<1	0	2	0
taste distortion	1	0	0	0
Central and Peripheral Nervous Systems				
dizziness	11	3	4	4
paresthesias	<1	0	0	0
drowsiness	<1	2	2	2
Autonomic Nervous System				
nasal stuffiness	3	0	0	0
ejaculation failure	2	0	0	0
impotence	1	0	1	3
increased sweating	<1	0	0	0
Cardiovascular				
edema	1	0	0	0
postural hypotension	1	0	0	0
bradycardia	0	0	5	12
Respiratory				
dyspnea	2	0	1	2
Skin				
rash	1	0	0	0
Special Senses				
vision abnormality	1	0	0	0
vertigo	2	1	0	0

The adverse effects were reported spontaneously and are representative of the incidence of adverse effects that may be observed in a properly selected hypertensive patient population, i.e., a group excluding patients with bronchospastic disease, overt congestive heart failure, or other contraindications to beta-blocker therapy.

Clinical trials also included studies utilizing daily doses up to 2400 mg in more severely hypertensive patients. Certain of the side effects increased with increasing dose as shown in the table below which depicts the entire U.S. therapeutic trials data base for adverse reactions that are clearly or possibly dose related.

Labetalol HCl Daily Dose (mg)	**200**	**300**	**400**	**600**
Number of Patients	522	181	606	608
Dizziness (%)	2	3	3	3
Fatigue	2	1	4	4
Nausea	<1	0	1	2
Vomiting	0	0	<1	<1
Dyspepsia	1	0	2	1
Paresthesias	2	0	2	2
Nasal Stuffiness	1	1	2	2
Ejaculation Failure	0	2	1	2
Impotence	1	1	1	1
Edema	1	0	1	1

Labetalol HCl Daily Dose (mg)	**800**	**900**	**1200**	**1600**	**2400**
Number of Patients	503	117	411	242	175
Dizziness (%)	5	1	9	13	16
Fatigue	5	3	7	6	10
Nausea	4	0	7	11	19
Vomiting	<1	0	1	2	3
Dyspepsia	1	0	2	2	4

Labetalol HCl Daily Dose (mg) (cont.)	**800**	**900**	**1200**	**1600**	**2400**
Paresthesias	1	1	2	5	5
Nasal Stuffiness	2	2	4	5	6
Ejaculation Failure	3	0	4	3	5
Impotence	2	4	3	4	3
Edema	1	0	1	2	2

In addition, a number of other less common adverse events have been reported in clinical trials or the literature:

Cardiovascular Postural hypotension, including rarely, syncope.

Central and Peripheral Nervous Systems Paresthesias, most frequently described as scalp tingling. In most cases, it was mild, transient and usually occurred at the beginning of treatment.

Collagen Disorders Systemic lupus erythematosus; positive antinuclear factor (ANF).

Eyes Dry eyes.

Immunological System Antimitochondrial antibodies.

Liver and Biliary System Cholestasis with or without jaundice.

Musculo-Skeletal System Muscle cramps; toxic myopathy.

Respiratory System Bronchospasm.

Skin and Appendages Rashes of various types, such as generalized maculo-papular; lichenoid; urticarial; bullous lichen planus; psoriaform; facial erythema; Peyronie's disease; reversible alopecia.

Urinary System Difficulty in micturition, including acute urinary bladder retention.

Following approval for marketing in the United Kingdom, a monitored release survey involving approximately 6,800 patients was conducted for further safety and efficacy evaluation of this product. Results of this survey indicate that the type, severity, and incidence of adverse effects were comparable to those cited above.

Potential Adverse Effects

In addition, other adverse effects not listed above have been reported with other beta-adrenergic blocking agents.

Central Nervous System Reversible mental depression progressing to catatonia; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Cardiovascular Intensification of AV block. See **CONTRAINDICATIONS.**

Allergic Fever combined with aching and sore throat; laryngospasm; respiratory distress.

Hematologic Agranulocytosis; thrombocytopenic or nonthrombocytopenic purpura.

Gastrointestinal Mesenteric artery thrombosis; ischemic colitis.

The oculomucocutaneous syndrome associated with the beta-blocker practolol has not been reported with labetalol HCl.

Clinical laboratory tests: There have been reversible increases of serum transaminases in 4% of patients treated with labetalol HCl and tested, and more rarely, reversible increases in blood urea.

OVERDOSAGE

Overdosage with NORMODYNE (labetalol HCl) Tablets causes excessive hypotension which is posture sensitive, and sometimes, excessive bradycardia. Patients should be laid supine and their legs raised if necessary to improve the blood supply to the brain. The following additional measures should be employed if necessary: Excessive *bradycardia* — administer atropine (3.0 mg). If there is no response to vagal blockade, administer isoproterenol cautiously. *Cardiac failure* — administer a digitalis glycoside and a diuretic. *Hypotension* — administer vasopressors, e.g., norepinephrine. There is pharmacological evidence that norepinephrine may be the drug of choice. *Bronchospasm* — administer a $beta_2$-stimulating agent and/or a theophylline preparation.

Gastric lavage or pharmacologically induced emesis (using syrup of ipecac) is useful for removal of the drug shortly after ingestion. Labetalol HCl can be removed from the general circulation by hemodialysis.

The oral LD_{50} value of labetalol HCl in the mouse is approximately 600 mg/kg and in the rat is greater than 2 gm/kg. The intravenous LD_{50} in these species is 50 to 60 mg/kg.

DOSAGE AND ADMINISTRATION

DOSAGE MUST BE INDIVIDUALIZED. The recommended initial dose is 100 mg twice daily whether used alone or added to a diuretic regimen. After 2 or 3 days, using standing blood pressure as an indicator, dosage may be titrated in increments of 100 mg bid every 2 or 3 days. The usual maintenance dosage of labetalol HCl is between 200 and 400 mg twice daily.

Since the full antihypertensive effect of labetalol HCl is usually seen within the first one to three hours of the initial dose or dose increment, the assurance of a lack of an exaggerated hypotensive response can be clinically established in the office setting. The antihypertensive effects of continued dosing can be measured at subsequent visits, approximately 12 hours after a dose, to determine whether further titration is necessary.

Patients with severe hypertension may require from 1200 mg to 2400 mg per day, with or without thiazide diuretics. Should side effects (principally nausea or dizziness) occur with these doses administered bid, the same total daily dose administered three times daily may improve tolerability and facilitate further titration. Titration increments should not exceed 200 mg twice daily.

When a diuretic is added, an additive antihypertensive effect can be expected. In some cases this may necessitate a labetalol HCl dosage adjustment. As with most antihypertensive drugs, optimal dosages of NORMODYNE Tablets are usually lower in patients also receiving a diuretic.

When transferring patients from other antihypertensive drugs, NORMODYNE Tablets should be introduced as recommended and the dosage of the existing therapy progressively decreased.

HOW SUPPLIED

NORMODYNE (labetalol HCl) Tablets, 100 mg, light-brown, round, scored, film-coated tablets engraved on one side with Schering and product identification numbers 244, and on the other side the number 100 for the strength and "NORMODYNE"; bottles of 100 (NDC-0085-0244-04), 500 (NDC-0085-0244-05), and box of 100 for unit-dose dispensing (NDC-0085-0244-08).

NORMODYNE (labetalol HCl) Tablets, 200 mg, white, round, scored, film-coated tablets engraved on one side with Schering and product identification numbers 752, and on the other side the number 200 for the strength and "NORMODYNE"; bottles of 100 (NDC-0085-0752-04), 500 (NDC-0085-0752-05), box of 100 for unit-dose dispensing (NDC-0085-0752-08), and Patient Calendar Package of 56 (4 bottles of 14 tablets) (NDC-0085-0752-03).

NORMODYNE (labetalol HCl) Tablets, 300 mg, blue, round, film-coated tablets engraved on one side with Schering and product identification numbers 438, and on the other side the number 300 for the strength and "NORMODYNE"; bottles of 100 (NDC-0085-0438-03), 500 (NDC-0085-0438-05), box of 100 for unit-dose dispensing (NDC-0085-0438-06), and Patient Calendar Package of 56 (4 bottles of 14 tablets) (NDC-0085-0438-02).

NORMODYNE (labetalol HCl) Tablets should be stored between 2° and 30°C (36° and 86°F).

NORMODYNE (labetalol HCl) Tablets in the unit-dose boxes should be protected from excessive moisture.

For complete prescribing information, please consult package insert.

Key Pharmaceuticals, Inc.
Kenilworth, NJ 07033 USA

Revised 3/85

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First hundreds...
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Soon more than a million.
Soon more than a million insulin users will be taking Humulin.
And no wonder. Humulin is identical to the insulin produced by the human pancreas—except that it is made by rDNA technology.
Humulin is not derived from animal pancreases. So it contains none of the animal-source pancreatic impurities that may contribute to insulin allergies or immunogenicity.
The clinical significance of insulin antibodies in the complications of diabetes is uncertain at this time. However, high antibody titers have been shown to decrease the small amounts of endogenous insulin secretion some insulin users still have. The lower immunogenicity of Humulin has been shown to result in lower insulin antibody titers; thus, Humulin may help to prolong endogenous insulin production in some patients.
Any change of insulin should be made cautiously and only under medical supervision. Changes in refinement, purity, strength, brand (manufacturer), type (regular, NPH, Lente®, etc), species/source (beef, pork, beef-pork, or human), and/or method of manufacture (recombinant DNA versus animal-source insulin) may result in the need for a change in dosage.
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In Memoriam

California Medical Association

Atkins, Charles E., Fresno. Died Dec 16, 1987, aged 88. Graduate of College Osteopathic P & S, 1928. Licensed in California in 1928. Dr Atkins was a member of the Fresno-Madera Medical Society.

Baker, Caroline, San Anselmo. Died Feb 6, 1988, aged 55. Graduate of Louisiana State University, New Orleans, 1965. Dr Baker was a member of the Marin Medical Society.

Blanchard, John P., Santa Barbara. Died Nov 11, 1987, aged 71. Graduate of Albany Medical College, Albany, New York, 1942. Dr Blanchard was a member of the Santa Barbara County Medical Society.

Chess, Stephen J., Ventura. Died Jan 11, 1988, aged 73. Dr Chess was a member of the Ventura County Medical Society.

Christopher, Howard W., San Jose. Died Dec 6, 1987, aged 66. Graduate of Stanford University School of Medicine, Stanford, California, 1955. Dr Christopher was a member of the Santa Clara County Medical Society.

Clavin, Ronald N., Los Angeles. Died Nov 23, 1987, aged 47. Graduate of Tulane University School of Medicine, New Orleans. Licensed in California in 1966. Dr Clavin was a member of the Los Angeles County Medical Association.

Dickson, Owen C., Berkeley. Died Dec 22, 1987, aged 75. Graduate of University of California, San Francisco, School of Medicine, 1939. Dr Dickson was a member of the Alameda-Contra Costa Medical Association.

Dooley, Richard R., San Bernardino. Died Feb 8, 1988, aged 63. Graduate of Long Island College of Medicine, Brooklyn, New York, 1947. Dr Dooley was a member of the San Bernardino County Medical Society.

Eliassen, George W., Oakland. Died Dec 10, 1987, aged 71. Graduate of University of California, San Francisco, School of Medicine, 1942. Dr Eliassen was a member of the Alameda-Contra Costa Medical Association.

Hause, Donald P., Sacramento. Died Nov 26, 1987, aged 69. Graduate of Marquette University, Milwaukee, 1942. Licensed in California in 1943. Dr Hause was a member of the Sacramento-El Dorado Medical Society.

Heath, Richard S., Los Angeles. Died Nov 27, 1987, aged 76. Graduate of University of Nebraska College of Medicine, Omaha. Licensed in California in 1938. Dr Heath was a member of the Los Angeles County Medical Association.

Helgesen, Robert M., San Mateo. Died Jan 10, 1988, aged 62. Graduate of Stanford University School of Medicine, Stanford, California, 1954. Dr Helgesen was a member of the San Mateo County Medical Society.

Henrich, Alfred G., Los Angeles. Died Nov 16, 1987, aged 85. Graduate of Washington University, St Louis. Dr Henrich was a member of the Los Angeles County Medical Association.

Josephson, J. Bernard, San Jose. Died Jan 5, 1988, aged 86. Graduate of University of California, San Francisco, School of Medicine, 1929. Dr Josephson was a member of the Santa Clara County Medical Society.

Kupka, Edward, Berkeley. Died Nov 15, 1987, aged 84. Graduate of Wayne State University School of Medicine, Detroit. Dr Kupka was a member of the Alameda-Contra Costa Medical Association.

Lyman, Richard W., Berkeley. Died Dec 14, 1987, aged 78. Graduate of University of Oregon School of Medicine, Portland, 1939. Dr Lyman was a member of the Alameda-Contra Costa Medical Association.

Masters, John H., Berkeley. Died Nov 5, 1987, aged 75. Graduate of McGill University Faculty of Medicine, Montreal, Quebec, 1947. Dr Masters was a member of the Alameda-Contra Costa Medical Association.

Mello, Henry G., Vallejo. Died Dec 22, 1987, aged 78. Graduate of Marquette University Medical School, Milwaukee, 1936. Dr Mello was a member of the Solano County Medical Society.

Obeji, Edward J., Los Angeles. Died Dec 5, 1987, aged 66. Graduate of Faculty of Medicine, Baghdad University. Dr Obeji was a member of the Los Angeles Medical Association.

Parkinson, Stanley R., Marysville. Died Jan 1988, aged 84. Graduate of Washington University, St Louis, 1934. Dr Parkinson was a member of the Yuba-Sutter-Colusa County Medical Society.

Patching, Frederick E., Berkeley. Died Jan 4, 1988, aged 65. Graduate of Stanford University School of Medicine, Stanford, California, 1952. Dr Patching was a member of the Alameda-Contra Costa Medical Association.

Richardson, W. A., Los Angeles. Died Dec 30, 1987, aged 87. Graduate of Loma Linda School of Medicine. Licensed in California in 1936. Dr Richardson was a member of the Los Angeles County Medical Association.

Shenk, Morris J., Oakland. Died Nov 19, 1987, aged 65. Graduate of Indiana University School of Medicine, Indianapolis, 1950. Dr Shenk was a member of the Alameda-Contra Costa Medical Association.

Simmons, Hugh M., Sacramento. Died Nov 19, 1987, aged 78. Graduate of University of Colorado School of Medicine, Denver, 1935. Dr Simmons was a member of the Sacramento-El Dorado Medical Society.

Stanton, Elvin H., Los Angeles. Died Dec 6, 1987, aged 79. Graduate of Loma Linda School of Medicine. Licensed in California in 1933. Dr Stanton was a member of the Los Angeles County Medical Association.

Stearns, Alexander L., Palm Springs. Died Dec 7, 1987, aged 83. Graduate of University of Illinois College of Medicine, Chicago. Dr Stearns was a member of the Riverside County Medical Association.

(Continued on Page 598)

CARAFATE®
(sucralfate) Tablets

BRIEF SUMMARY

CONTRAINDICATIONS
There are no known contraindications to the use of sucralfate

PRECAUTIONS
Duodenal ulcer is a chronic, recurrent disease While short-term treatment with sucralfate can result in complete healing of the ulcer, a successful course of treatment with sucralfate should not be expected to alter the post-healing frequency or severity of duodenal ulceration

Drug Interactions: Animal studies have shown that simultaneous administration of CARAFATE (sucralfate) with tetracycline, phenytoin, digoxin, or cimetidine will result in a statistically significant reduction in the bioavailability of these agents The bioavailability of these agents may be restored simply by separating the administration of these agents from that of CARAFATE by two hours. This interaction appears to be nonsystemic in origin, presumably resulting from these agents being bound by CARAFATE in the gastrointestinal tract The clinical significance of these animal studies is yet to be defined However, because of the potential of CARAFATE to alter the absorption of some drugs from the gastrointestinal tract, the separate administration of CARAFATE from that of other agents should be considered when alterations in bioavailability are felt to be critical for concomitantly administered drugs

Carcinogenesis, Mutagenesis, Impairment of Fertility: Chronic oral toxicity studies of 24 months' duration were conducted in mice and rats at doses up to 1 gm/kg (12 times the human dose) There was no evidence of drug-related tumorigenicity A reproduction study in rats at doses up to 38 times the human dose did not reveal any indication of fertility impairment Mutagenicity studies were not conducted

Pregnancy: Teratogenic effects Pregnancy Category B Teratogenicity studies have been performed in mice, rats, and rabbits at doses up to 50 times the human dose and have revealed no evidence of harm to the fetus due to sucralfate There are, however, no adequate and well-controlled studies in pregnant women Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed

Nursing Mothers: It is not known whether this drug is excreted in human milk Because many drugs are excreted in human milk, caution should be exercised when sucralfate is administered to a nursing woman

Pediatric Use: Safety and effectiveness in children have not been established

ADVERSE REACTIONS
Adverse reactions to sucralfate in clinical trials were minor and only rarely led to discontinuation of the drug In studies involving over 2,500 patients treated with sucralfate, adverse effects were reported in 121 (4 7%)

Constipation was the most frequent complaint (2 2%) Other adverse effects, reported in no more than one of every 350 patients, were diarrhea, nausea, gastric discomfort, indigestion, dry mouth, rash, pruritus, back pain, dizziness, sleepiness, and vertigo

OVERDOSAGE
There is no experience in humans with overdosage Acute oral toxicity studies in animals, however, using doses up to 12 gm/kg body weight, could not find a lethal dose Risks associated with overdosage should, therefore, be minimal

DOSAGE AND ADMINISTRATION
The recommended adult oral dosage for duodenal ulcer is 1 gm four times a day on an empty stomach

Antacids may be prescribed as needed for relief of pain but should not be taken within one-half hour before or after sucralfate

While healing with sucralfate may occur during the first week or two, treatment should be continued for 4 to 8 weeks unless healing has been demonstrated by x-ray or endoscopic examination

HOW SUPPLIED
CARAFATE (sucralfate) 1-gm tablets are supplied in bottles of 100 (NDC 0088-1712-47) and in Unit Dose Identification Paks of 100 (NDC 0088-1712-49) Light pink scored oblong tablets are embossed with CARAFATE on one side and 1712 bracketed by C's on the other

Issued 1/87

References:
1 Korman MG, Shaw RG, Hansky J, et al: *Gastroenterology* 80:1451-1453, 1981
2 Korman MG, Hansky J, Merrett AC, et al: *Dig Dis Sci* 27:712-715, 1982
3 Brandstaetter G, Kratochvil P: *Am J Med* 79 (suppl 2C):36-38, 1985
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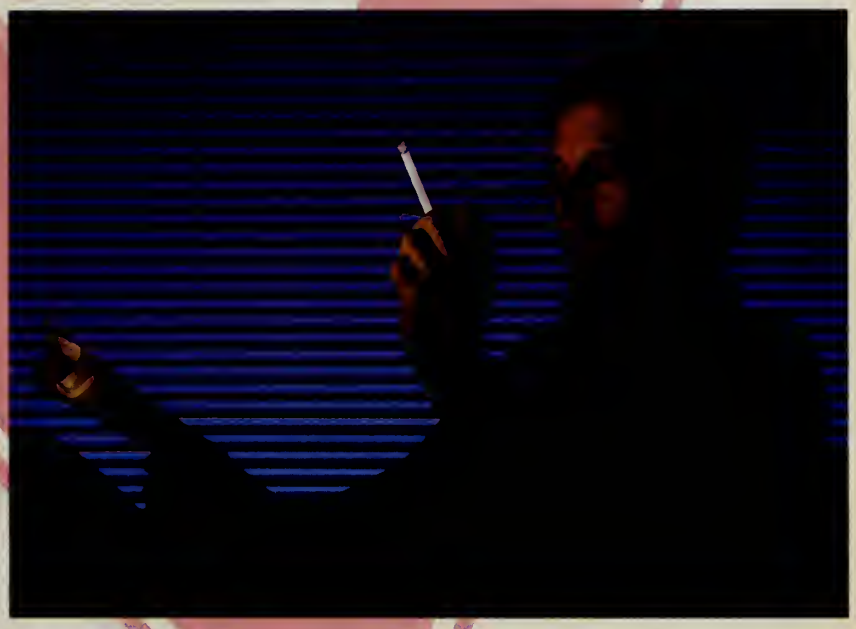
Ulcer therapy that won't yield, even to smoking



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Cimetidine:	
All patients	76.3%
Smokers	62.5%

*Significantly greater than cimetidine smoker group ($P < .05$).

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The portrait of anxiety

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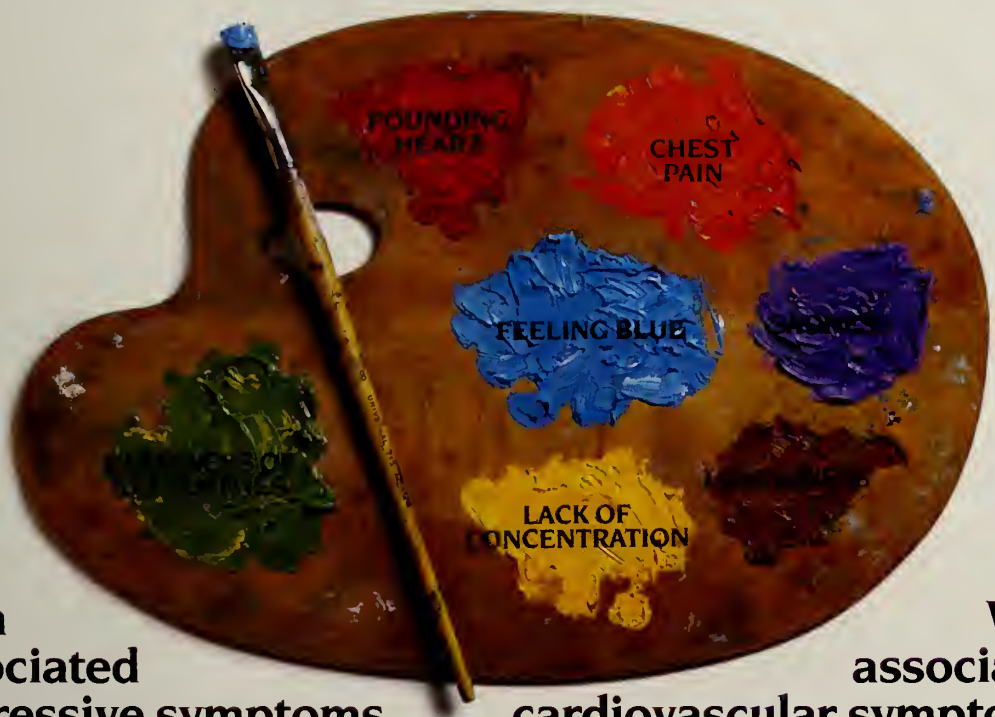
is often complicated



With associated depressive symptoms.

In double-blind, four-week clinical trials in 632 patients with moderate to severe anxiety, therapy with XANAX was compared with placebo.

XANAX was significantly more effective ($P<.001$) than placebo in relieving the anxiety, with over half of the patients showing marked to moderate improvement by the first evaluation period (one week).

In addition, over 70% of these patients experienced associated moderate to severe depressed mood. XANAX was shown to be significantly more effective ($P<.014$) than placebo in improving the associated depressed mood.

With associated cardiovascular symptoms.

Almost 60% of patients in the study had anxiety with associated cardiovascular symptoms even though cardiovascular disease had been ruled out. XANAX was shown to effectively relieve anxiety including the associated cardiovascular symptoms.

XANAX, the first of a unique class—the triazolobenzodiazepines.

- *Well tolerated*—Side effects, if they occur, are generally observed at the beginning of therapy and usually disappear with continued medication. Drowsiness and light-headedness were the most commonly reported adverse reactions.
- *Sustained efficacy*—No reported increase in dosage during 16-week clinical study, once an appropriate dosage was achieved. Since long-term effectiveness of XANAX has not been established, it is recommended that it not be used for longer than 16 weeks.
- *Simple dosage*—0.25 to 0.5 mg t.i.d.

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alprazolam IV

for the relief of complicated anxiety

XANAX® Tablets
(alprazolam)

INDICATIONS AND USAGE
Anxiety disorders, short-term relief of the symptoms of anxiety, and anxiety associated with depression. Anxiety or tension associated with the stress of everyday life usually does not require an anxiolytic. Effectiveness for more than four months has not been established; periodically reassess the usefulness of the drug for the individual patient.

CONTRAINDICATIONS
Sensitivity to XANAX or other benzodiazepines, and in acute narrow angle glaucoma.

WARNINGS
Benzodiazepines can cause fetal harm in pregnant women, hence women who may become pregnant should be warned. Avoid during the first trimester. Withdrawal seizures have been reported upon rapid dose reduction or abrupt discontinuation, thus reduce dose gradually. (See Drug Abuse and Dependence and Dosage and Administration.)

PRECAUTIONS
General: If XANAX is combined with other psychotropics or anticonvulsants, consider drug potentiation. (See Drug Interactions). Use the usual precautions in patients with renal or hepatic impairment and regarding prescription size in depressed and suicidal patients. In elderly and debilitated patients, use the lowest possible dose. (See Dosage and Administration.) Hypomania and mania has been reported in depressed patients.
Information for Patients: Alert patients about: (a) consumption of alcohol and drugs, (b) possible fetal abnormalities, (c) operating machinery or driving, (d) not increasing dose of the drug due to risk of dependence, (e) not stopping the drug abruptly. *Laboratory Tests*: Not ordinarily required in otherwise healthy patients. *Drug Interactions*: Additive CNS depressant effects with other psychotropics, anticonvulsants, antihistamines, ethanol and other CNS depressants. Plasma levels of imipramine and desipramine are increased. Pharmacokinetic interactions with other drugs have been reported. Cimetidine can delay clearance of benzodiazepines. *Drug/Laboratory Test Interactions*: No consistent pattern for a drug or test. *Carcinogenesis, Mutagenesis, Impairment of Fertility*: No carcinogenic potential or impairment of fertility in rats. *Pregnancy*: See Warnings. *Nonteratogenic Effects*: The child born of a mother on benzodiazepines may be at some risk for withdrawal symptoms, neonatal flaccidity and respiratory problems. *Labor and Delivery*: No established use. *Nursing Mothers*: Benzodiazepines are excreted in human milk. Women on XANAX should not nurse. *Pediatric Use*: Safety and effectiveness in children below the age of 18 have not been established.

ADVERSE REACTIONS
Side effects are generally observed at the beginning of therapy and usually disappear with continued medication. In the usual patient, the most frequent side effects are likely to be an extension of the pharmacologic activity of XANAX, e.g., drowsiness or lightheadedness.
Central nervous system: Drowsiness, lightheadedness, depression, headache, confusion, insomnia, nervousness, syncope, dizziness, akathisia, and tiredness/sleepiness. *Gastrointestinal*: Dry mouth, constipation, diarrhea, nausea/vomiting, and increased salivation. *Cardiovascular*: Tachycardia/palpitations, and hypotension. *Sensory*: Blurred vision. *Musculoskeletal*: Rigidity and tremor. *Cutaneous*: Dermatitis/allergy. *Other side effects*: Nasal congestion, weight gain, and weight loss.
Withdrawal seizures with rapid decrease or abrupt discontinuation. (See Warnings.)
The following adverse events have been reported with benzodiazepines: dystonia, irritability, concentration difficulties, anorexia, transient amnesia or memory impairment, loss of coordination, fatigue, seizures, sedation, slurred speech, jaundice, musculoskeletal weakness, pruritus, diplopia, dysarthria, changes in libido, menstrual irregularities, incontinence, and urinary retention.
Paradoxical reactions such as stimulation, agitation, rage, increased muscle spasticity, sleep disturbances, and hallucinations may occur. Should these occur, discontinue the drug.
During prolonged treatment, periodic blood counts, urinalysis, and blood chemistry analysis are advisable. Minor EEG changes, of unknown significance, have been observed.
Liver enzyme elevations, gynecomastia and galactorrhea have been reported but no causal relationship was established.

DRUG ABUSE AND DEPENDENCE
Physical and Psychological Dependence: Withdrawal symptoms including seizures have occurred following abrupt discontinuance or rapid dose reduction of benzodiazepines. (See Warnings). Dosage should be gradually tapered under close supervision. Patients with a history of seizures or epilepsy should not be abruptly withdrawn from XANAX. Addiction-prone individuals should be under careful surveillance. *Controlled Substance Class*: XANAX is a controlled substance and has been assigned to schedule IV.

OVERDOSAGE
Manifestations include somnolence, confusion, impaired coordination, diminished reflexes and coma. No delayed reactions have been reported.

DOSAGE AND ADMINISTRATION
Dosage should be individualized.
The usual starting dose is 0.25 to 0.5 mg, t.i.d. Maximum total daily dose is 4 mg. In the elderly or debilitated, the usual starting dose is 0.25 mg, two or three times daily. Reduce dosage gradually when terminating therapy, by no more than 0.5 mg every three days.

HOW SUPPLIED
XANAX Tablets are available as 0.25 mg, 0.5 mg, and 1 mg tablets.

CAUTION:
FEDERAL LAW PROHIBITS DISPENSING WITHOUT PRESCRIPTION. B-7-S

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Kalamazoo, Michigan 49001, USA April 1988

CONTINUING MEDICAL EDUCATION

(Continued from Page 530)

November 3-5—**New Directions in Anti-viral Chemotherapy.** UCSF at Hyatt on Union Square, San Francisco. Thurs-Sat. $100. Contact: UCSF.

OB/GYN

June 3—**Contemporary Concepts in Reproductive Health Care.** Planned Parenthood at Holiday Inn Fisherman's Wharf, San Francisco. Fri. Contact: Lisa Aronow. (415) 441-7858.

June 30-July 3—**6th Annual Controversies in Obstetrics & Gynecology.** Center for Health Education at Mauna Kea Beach Hotel, Hawaii. Thur-Sun. Contact: The Center for Health Education, 2081 Atlantic Ave., PO Box 1428, Long Beach, 90801-1428. (213) 595-3811.

August 19-21—**1988—Office Gynecology for the Primary Care Physician.** Continuing Medical Education Associates and San Diego State University at Hyatt Islandia, San Diego. Fri-Sun. 18 hrs. $295. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

November 10-13—**Current Issues in Perinatal Medicine.** UCI at Marriott's Rancho Las Palmas Resort, Palm Springs. Thurs-Sat. Contact: UCI.

November 13-19—**11th Annual Review Course in Clinical Obstetrics & Gynecology.** The Center for Health Education at Westin South Coast Plaza Hotel, Costa Mesa. Sun-Sat. Contact: The Center for Health Education, 2081 Atlantic Ave., PO Box 1428, Long Beach, 90801-1428. (213) 595-3811.

PEDIATRICS

May 21—**4th Annual Spring Meeting Adolescent Symposium and Neil Minkoff, MD, Memorial Lecture.** Los Angeles Pediatric Society at Marina Beach Hotel, Marina del Rey. Sat. 6 hrs. $75. Contact: Los Angeles Pediatric Society, PO Box 2022, Inglewood 90305. (213) 757-1198.

June 24-25—**Current Concepts in Child Neurology 1988.** Children's Hospital San Diego at the Holiday Inn Montgomery Field, San Diego. Fri-Sat. 10 hrs. Contact: Continuing Medical Education Office, Children's Hospital. (619) 576-4072.

August 22-24—**Pediatrics Update: 1988.** San Diego State University at Hyatt Islandia, San Diego. Mon-Wed. 18 hrs. $295. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

October 15-20—**American Academy of Pediatrics Annual Session.** AAP. Sat-Thurs. Contact: AAP, 1801 Hinman Ave., Evanston, IL 60201.

October 22-29—**13th Annual Pediatrics for the Practitioner: A Pediatric Symposium.** Center for Health Education at Mauna Kea Beach Hotel, Hawaii. One week. Contact: The Center for Health Education, PO Box 1428, Long Beach 90801-1428.

PSYCHIATRY

May 23-24—**Child Abuse.** UCD at Holiday Inn Holidome, Sacramento. Mon-Tue. Contact: UCD.

June 8-10—**6th Annual Training Institute.** Northern California Group Therapy Society at Asilomar Conference Center, Pacific Grove. Wed-Fri. 12 hrs. $120. Contact: NCGPS Administrator, Marie Hayward, PO Box 229, Tiburon 94920. (415) 435-4150.

June 10-12—**31st Annual Clinical Conference.** Northern California Group Psychotherapy Society at Asilomar Conference Center, Pacific Grove. Fri-Sun. 11 hrs. $90. Contact: NCGPS Administrator, Marie Hayward, PO Box 229, Tiburon 94920. (415) 435-4150.

November 18-20—**34th Annual Group Therapy Symposium.** UCSF. Fri-Sun. Contact: UCSF.

RADIOLOGY

July 16-17—**Two-Day Seminar in Breast Imaging with Interpretive Workshops.** Los Angeles Radiological Society at Registry Hotel, Universal City. Sat-Sun. 10 hrs. $200. Contact: LARS, PO Box 91215, Los Angeles 90009-1215. (213) 642-0921.

July 28-31—**Second Annual Symposium on Magnetic Resonance Imaging.** Hoag Memorial Hospital at Ritz-Carlton Hotel, Laguna Niguel. Thurs-Sun. $395. Contact: Mary J. Ryals and Associates, PO Box 920113, Norcross, GA 30092-0113. (404) 641-9773.

(Continued on Page 600)

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This drug is not indicated for initial therapy of edema or hypertension. Edema or hypertension requires therapy titrated to the individual. If this combination represents the dosage so determined, its use may be more convenient in patient management. Treatment of hypertension and edema is not static, but must be reevaluated as conditions in each patient warrant.

Contraindications: Concomitant use with other potassium-sparing agents such as spironolactone or amiloride. Further use in anuria, progressive renal or hepatic dysfunction, hyperkalemia. Pre-existing elevated serum potassium. Hypersensitivity to either component or other sulfonamide-derived drugs.
Warnings: Do not use potassium supplements, dietary or otherwise, unless hypokalemia develops or dietary intake of potassium is markedly impaired. If supplementary potassium is needed, potassium tablets should not be used. Hyperkalemia can occur, and has been associated with cardiac irregularities. It is more likely in the severely ill, with urine volume less than one liter/day, the elderly and diabetics with suspected or confirmed renal insufficiency. Periodically, serum K^+ levels should be determined. If hyperkalemia develops, substitute a thiazide alone, restrict K^+ intake. **Associated widened QRS complex or arrhythmia requires prompt additional therapy.** Thiazides cross the placental barrier and appear in cord blood. Use in pregnancy requires weighing anticipated benefits against possible hazards, including fetal or neonatal jaundice, thrombocytopenia, other adverse reactions seen in adults. Thiazides appear and triamterene may appear in breast milk. If their use is essential, the patient should stop nursing. Adequate information on use in children is not available. Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma. Possible exacerbation or activation of systemic lupus erythematosus has been reported with thiazide diuretics.
Precautions: The bioavailability of the hydrochlorothiazide component of 'Dyazide' is about 50% of the bioavailability of the single entity. Theoretically, a patient transferred from the single entities of triamterene and hydrochlorothiazide may show an increase in blood pressure or fluid retention. Similarly, it is also possible that the lesser hydrochlorothiazide bioavailability could lead to increased serum potassium levels. However, extensive clinical experience with 'Dyazide' suggests that these conditions have not been commonly observed in clinical practice. Angiotensin-converting enzyme (ACE) inhibitors can elevate serum potassium; use with caution with 'Dyazide'. Do periodic serum electrolyte determinations (particularly important in patients vomiting excessively or receiving parenteral fluids, and during concurrent use with amphotericin B or corticosteroids or corticotropin[ACTH]). Periodic BUN and serum creatinine determinations should be made, especially in the elderly, diabetics or those with suspected or confirmed renal insufficiency. Cumulative effects of the drug may develop in patients with impaired renal function. Thiazides should be used with caution in patients with impaired hepatic function. They can precipitate coma in patients with severe liver disease. Observe regularly for possible blood dyscrasias, liver damage, other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving triamterene, and leukopenia, thrombocytopenia, agranulocytosis, and aplastic and hemolytic anemia have been reported with thiazides. Thiazides may cause manifestation of latent diabetes mellitus. The effects of oral anticoagulants may be decreased when used concurrently with hydrochlorothiazide; dosage adjustments may be necessary. Clinically insignificant reductions in arterial responsiveness to norepinephrine have been reported. Thiazides have also been shown to increase the paralyzing effect of nondepolarizing muscle relaxants such as tubocurarine. Triamterene is a weak folic acid antagonist. Do periodic blood studies in cirrhotics with splenomegaly. Antihypertensive effects may be enhanced in post-sympathectomy patients. Use cautiously in surgical patients. Triamterene has been found in renal stones in association with the other usual calculus components. Therefore, 'Dyazide' should be used with caution in patients with histories of stone formation. A few occurrences of acute renal failure have been reported in patients on 'Dyazide' when treated with indomethacin. Therefore, caution is advised in administering nonsteroidal anti-inflammatory agents with 'Dyazide'. The following may occur: transient elevated BUN or creatinine or both, hyperglycemia and glycosuria (diabetic insulin requirements may be altered), hyperuricemia and gout, digitalis intoxication (in hypokalemia), decreasing alkali reserve with possible metabolic acidosis. 'Dyazide' interferes with fluorescent measurement of quinidine. Hypokalemia is uncommon with 'Dyazide', but should it develop, corrective measures should be taken such as potassium supplementation or increased dietary intake of potassium-rich foods. Corrective measures should be instituted cautiously and serum potassium levels determined. Discontinue corrective measures and 'Dyazide' should laboratory values reveal elevated serum potassium. Chloride deficit may occur as well as dilutional hyponatremia. Concurrent use with chlorpropamide may increase the risk of severe hyponatremia. Serum PBI levels may decrease without signs of thyroid disturbance. Calcium excretion is decreased by thiazides. 'Dyazide' should be withdrawn before conducting tests for parathyroid function. Thiazides may add to or potentiate the action of other antihypertensive drugs. Diuretics reduce renal clearance of lithium and increase the risk of lithium toxicity.
Adverse Reactions: Muscle cramps, weakness, dizziness, headache, dry mouth; anaphylaxis, rash, urticaria, photosensitivity, purpura, other dermatological conditions; nausea and vomiting, diarrhea, constipation, other gastrointestinal disturbances; postural hypotension (may be aggravated by alcohol, barbiturates, or narcotics). Necrotizing vasculitis, paresthesias, icterus, pancreatitis, xanthopsia and respiratory distress including pneumonitis and pulmonary edema, transient blurred vision, sialadenitis, and vertigo have occurred with thiazides alone. Triamterene has been found in renal stones in association with other usual calculus components. Rare incidents of acute interstitial nephritis have been reported. Impotence has been reported in a few patients on 'Dyazide', although a causal relationship has not been established.
Supplied: 'Dyazide' is supplied as a red and white capsule, in bottles of 1000 capsules; Single Unit Packages (unit-dose) of 100 (intended for institutional use only); in Patient-Pak™ unit-of-use bottles of 100.

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Clinical Investigation

Acetazolamide and Dexamethasone in the Prevention of Acute Mountain Sickness

STEVEN C. ZELL, MD, *and* PHILIP H. GOODMAN, MD, *Reno, Nevada*

We randomly assigned 32 healthy backpackers to receive placebo, acetazolamide (250 mg twice a day), dexamethasone acetate (4 mg four times a day), or both drugs in combination to determine the drug efficacy in preventing acute mountain sickness (AMS) at altitudes of 3,650 to 4,050 m (12,000 to 13,300 ft). The incidence of AMS was high but symptoms were generally mild. Combined drug therapy was superior to both placebo and single drug therapy in risk reduction. Using acetazolamide alone was moderately beneficial in preventing the occurrence of AMS, although minor side effects were frequent. The use of dexamethasone alone did not significantly reduce the AMS incidence, and discontinuing its use resulted in symptoms suggestive of adrenal insufficiency. For recreational backpackers, routine drug prophylaxis is not recommended, in view of the mild nature of this illness and the adverse effects of medications. The efficacy of combined acetazolamide-dexamethasone therapy warrants further investigation at higher altitudes, where AMS is more severe, and the dexamethasone should be withdrawn gradually to avoid a possible adrenal crisis.

(Zell SC, Goodman PH: Acetazolamide and dexamethasone in the prevention of acute mountain sickness. West J Med 1988 May; 148:541-545)

Acute mountain sickness (AMS) is a mild form of high altitude illness experienced by persons who rapidly ascend to altitudes above 2,400 m (8,000 ft).[1] Among its unique constellation of symptoms, headache, light-headedness, nausea, anorexia, and insomnia predominate.[2,3] Although rarely serious, AMS can be unpleasant, making the wilderness experience a miserable one. In light of the growing interest in wilderness medicine and the increasing number of recreationalists visiting high-altitude areas,[4] attention has been directed toward prophylactic drug therapy.[5-8] Studies conducted at altitudes above 4,500 m (15,000 ft) suggest the frequency of AMS to be high.[6-8] Because most recreational backpackers spend their time at elevations of 3,000 to 3,600 m (10,000 to 12,000 ft), however, the incidence of AMS may be lower. Drug prophylaxis may be difficult to justify, especially if the medications prescribed are associated with adverse side effects.

Over the past decade, the pathophysiology of AMS has become better understood. Arterial oxygen content decreases with higher altitudes, resulting in hyperventilation and a pronounced respiratory alkalosis that limits the medullary respiratory center's response to fully compensate for hypoxemia.[2,9,10] The resultant pulmonary hypertension makes the lungs susceptible to a high-protein, high-permeability capillary leak syndrome.[11-13] After two to five days at a high altitude, renal bicarbonate excretion partially corrects this acid-base disturbance, permitting increased alveolar ventilation. Administering acetazolamide hastens this excretion, thereby improving arterial oxygenation and ventilatory response at high altitudes. The use of this drug has been shown to alleviate the symptoms of AMS effectively in several randomized studies.[6-8,14,15]

Attention has recently been given to the possible role of cerebral edema in producing the symptoms of AMS. At high altitudes, cerebral vasodilation occurs, leading to increased plasma filtration and gross cerebral edema.[6,16] These changes are exacerbated by derangements in the body's handling of water,[17,18] which is characteristic of high-altitude cerebral edema. It is unclear whether such abnormalities play a role in producing the mild to moderate headache of AMS. Dexamethasone acetate, a potent synthetic glucocorticoid valuable in the management of cerebral edema,[19] was given prophylactically in one study to subjects exposed to simulated high altitudes. Although the severity of AMS was mild, the investigators reported favorable results and no adverse side effects.[5] The subjects, however, were sedentary and the effects that stress and vigorous physical exercise might have on the body's response to this potent glucocorticoid could not be ascertained. In addition, there was no record that gross cerebral edema was present.

Despite evidence that acetazolamide and dexamethasone may reduce the risk of AMS, these drugs have not been prospectively studied in combination to determine if their benefits are additive or synergistic.

We conducted a double-blind prospective study to investigate the efficacy of acetazolamide and dexamethasone in preventing AMS, specifically to determine the following: the incidence of AMS in recreational climbers to moderate altitudes; the prophylactic benefit of the two drugs, alone and in combination; and the safety profile of administering dexa-

From the Department of Medicine, Veterans Administration Medical Center, University of Nevada School of Medicine, Reno.
Reprint requests to Steven C. Zell, MD, Department of Medicine, VA Medical Center, 1000 Locust St, Reno, NV 89520.

ABBREVIATIONS USED IN TEXT

AMS = acute mountain sickness
AMS-C = cerebral acute mountain sickness
AMS-R = respiratory acute mountain sickness
ESQ = Environmental Symptoms Questionnaire

methasone and acetazolamide under conditions of moderate altitudes and physical exertion.

Subjects and Methods

We recruited participants from an introductory backpacking class at the University of Nevada, Reno. These were novice backpackers having no previous history of AMS and no recent travel to high altitudes. Persons under the care of a physician for ongoing cardiopulmonary problems and those having a history of glucose intolerance or diabetes mellitus were excluded. A total of 32 adults (20 men, 12 women), ages 18 to 49 years, gave their informed consent to participate in the study. There were no clinically significant differences among mean ages of the treatment groups. All were instructed to take only their assigned medications and to refrain from the use of aspirin, over-the-counter medications, and alcohol. The study was approved by the University of Nevada's Human Subject Committee.

Participants were randomly assigned to one of four treatment groups, receiving either placebo, active acetazolamide, dexamethasone acetate, or both drugs in combination. Acetazolamide was taken twice a day at a dosage of 250 mg and dexamethasone in doses of 4 mg every six hours. Each subject received two vials of unmarked medications, one of which was taken twice a day and the other four times a day. Participants began taking their medications two days before an ascent and continued for 48 hours of high-altitude exposure.

On the evening before ascent, they drove from Reno at 1,340 m (4,400 ft) to a base camp at 2,100 m (7,000 ft). The following morning, they were shuttled by car to the Baker-Green Lake Trailhead at 2,700 m (9,000 ft) in the Sierra Nevada Mountains, from where they embarked on a strenuous six-mile backpack trip to an altitude of 3,650 m (12,000 ft). The participants remained active at that elevation for the duration of the study and on the second day took part in a nontechnical climb to an elevation of 4,050 m (13,300 ft). They slept at an altitude of 12,000 ft for two evenings during the study. Assessment of acute mountain sickness was based on the Environmental Symptoms Questionnaire (ESQ), which was administered at base camp and in the morning and evening at 12-hour intervals during high-altitude exposure. The ESQ is a 67-item questionnaire designed to provide a standardized measuring system for scoring AMS by distinguishing symptoms of AMS from others associated with the environmental stresses of climbing at high altitudes. A value ranging from 0 ("not at all") to 5 ("extreme") is assigned to each of 67 symptom responses, and a weighted average of cerebral symptoms (AMS-C) and respiratory symptoms (AMS-R) is derived from the scores.[20] The questionnaire has been previously used and validated clinically.[5,20]

Statistical Analysis

A relatively high proportion of participants were asymptomatic, resulting in raw ESQ scores that were heavily skewed to the right. Although the early prevalence of cerebral sickness in the placebo group was 50% and of respiratory sickness 75%, the severity of illness was low by ESQ criteria.[20] Furthermore, the relatively small size of the groups contributed to heteroscedasticity, which was not alleviated by standard algebraic transformations. For this reason, differences between altitude and base camp scores were compared with the severity index cutoff levels (AMS-C $=0.431$; AMS-R $=0.143$) proposed by Sampson and coworkers specifically for this circumstance—that is, treatment group size less than 30.[20] The number of those who were sick (index ≥ 1) and the number of those who were not (index $= 0$) by these criteria were compared by treatment group. This dichotomous assignment was justified by the finding that only one cerebral index in a placebo-treated subject, cerebral and respiratory indexes in another, and one acetazolamide-treated subject's respiratory index, were greater than one. Figure 1 shows the prevalence of AMS cases per treatment group at the time of each questionnaire. To control for con-

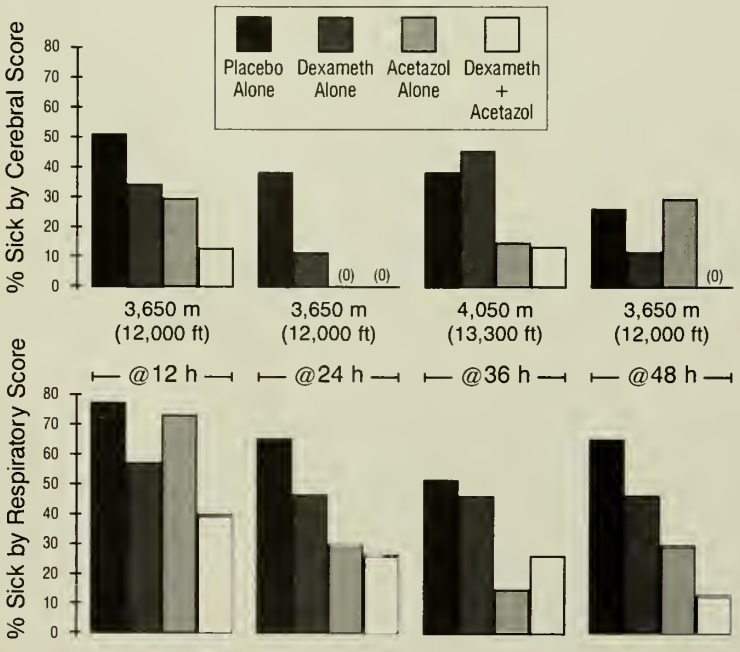

Figure 1.—The graphs show the prevalence of cerebral and respiratory acute mountain sickness at altitudes of 3,650 to 4,050 m (12,000 to 13,300 ft) within drug treatment groups at the four sequential administrations of the Environmental Symptoms Questionnaire. Pairwise analyses of treatments revealed that for both cerebral and respiratory scores, using the drug combination dexamethasone acetate and acetazolamide (Dexameth + Acetazol) was consistently superior to giving either placebo or dexamethasone (Dexameth) alone, and giving acetazolamide (Acetazol) was superior to giving placebo. Although pairwise comparison of the use of dexamethasone with that of placebo and with administering acetazolamide did not achieve isolated statistical significance at $P<.10$, stratified trend analyses for the direction of effects (dexamethasone plus acetazolamide > acetazolamide > dexamethasone > placebo) was significant for cerebral ($P = .002$) and respiratory ($P = .001$) scores independently.

founding factors such as changes in altitude, activity, or camp, pairwise stratified treatment effects were tested using the Mantel-Haenszel summary χ_{MH1}^2 analysis.[21] The linear trend of efficacy across drug treatments was tested across the four variables—altitude, activity, camp, and stratified pairs—using 2 (sick versus not sick) × 4 (treatments) tables according to the method of Mantel, including a correction for continuity.[22]

Because the goal of AMS prophylaxis is to reduce the overall incidence of symptoms among those ascending to high altitudes, the preventable fraction of disease was considered a more appropriate epidemiologic summary analysis than that of risk ratio. Figure 2 shows preventable fractions attributable to the effect of treatment (tx) over placebo (pl), calculated as $(I_{pl} - I_{tx})I_{pl}$, where I is the person-time incidence of sickness in a group, with confidence limits generated by a procedure analogous to that described by Fleiss for Levin's attributable risk.[23] All tests were two-tailed.

Results

Assessments conducted every 12 hours at altitudes above 3,650 m (12,000 ft) in those treated with either dexamethasone or acetazolamide, or both, generally showed a lower incidence of sickness than that found in the placebo-treated group (Figure 1). Compared with the use of placebo, the group given the combination of dexamethasone and acetazolamide had an average incidence of AMS-C of 6% versus 38% for placebo ($\chi_{MH1}^2 = 8.82$; $P = .004$) and an incidence of AMS-R of 25% versus 63% for placebo ($\chi_{MH1}^2 = 8.78$; $P = .004$). In the group given acetazolamide alone, there was an average incidence of AMS-C of 16% versus 38% ($\chi_{MH1}^2 = 4.37$; $P = .04$), and one of AMS-R of 31% versus 63% ($\chi_{MH1}^2 = 8.78$; $P = .09$). The reduction in sickness rate did not achieve statistical significance in those treated by dexamethasone alone ($P > .10$), but stratified trend analyses for the direction of effects (dexamethasone plus acetazolamide > acetazolamide > dexamethasone > placebo) were significant for both cerebral scores ($\chi_1^2 = 10.18$; $P = .002$) and respiratory scores ($\chi_1^2 = 10.58$; $P = .001$). The corresponding unstratified trend statistics were essentially the same (cerebral, $\chi_1^2 = 9.57$; respiratory, $\chi_1^2 = 10.06$), suggesting that altitude or activity at the four camps did not significantly confound the trend in the drug treatment effects.

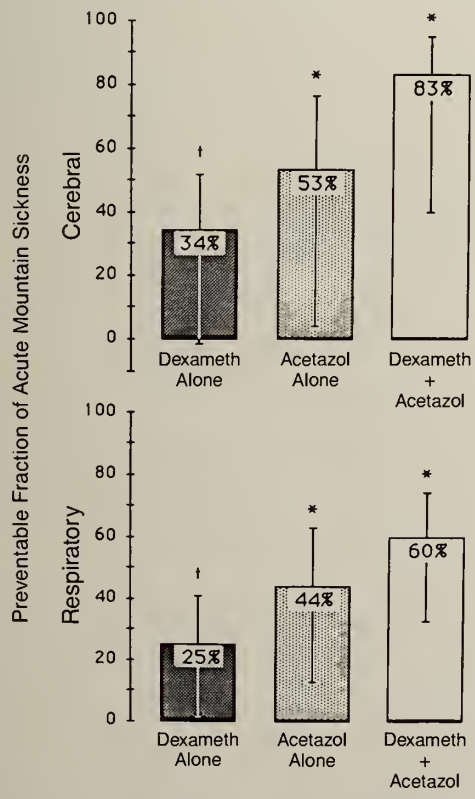

Figure 2.—The graphs show the preventable fraction of acute mountain sickness (AMS), expressed as the mean percent reduction of AMS risk potentially achievable through the use of each of the three treatment regimens compared with giving placebo. The bars delimit the 95% confidence limits of the mean preventable fraction (confidence limits are asymmetric around the mean because the preventable fraction is a ratio rather than a linear measure). Although confidence limits for the use of dexamethasone versus placebo include zero (no preventive effect), the major overlap is with positive values of preventable fractions. *Confidence limits indicate the range of positive preventable fractions likely to be determined in 95% of repetitive samples. †Confidence limits include zero.

The preventable fraction of disease is an epidemiologic measurement indicating the fraction of the incidence rate observed in placebo-treated subjects that would have been prevented if all had received the specified active treatment. The individual fractional reductions (Figure 2) for dexamethasone and acetazolamide given alone add up approximately to the effect the combined-drug treatment had in preventing the occurrence of AMS-C and AMS-R. This is compatible with an additive biologic effect for the two active drugs.

Side effects of drug treatment were readily separated into acetazolamide-associated and dexamethasone-associated symptoms. This division is supported by the virtual absence of symptoms among placebo recipients coupled with the coincidence of symptom clusters in the combined-therapy group (Table 1). Numbness and taste disturbances were common in those given acetazolamide alone. Fatigue after the trip, depression, and insomnia were reported by more than half of those receiving dexamethasone alone but not by any in the placebo or acetazolamide groups. Five of the seven subjects reporting depression after discontinuing the use of dexamethasone described, in open-ended responses, the depression as so severe that they would never want to take the medication again.

Discussion

In this study, ascent to a moderate altitude led to a significant incidence of mild acute mountain sickness, which can be reduced with drug prophylaxis. The benefits of such treatment, however, must be weighed against its side effects, which were frequent enough to preclude the routine use of acetazolamide or dexamethasone in the prophylaxis of AMS.

Hackett and associates in a review of numerous studies on AMS cited incidence rates of up to 53%.[6] Although our study was conducted at lower altitudes, we observed a similar incidence of both AMS-C and AMS-R, while the latter occurred more frequently. Nevertheless, the degree of illness observed in our study population was mild. Thus, of the 18 who were ill, only three scored 2.0 or higher on a severity scale up to 10.0. The rest had a score of 1.0, the lowest level at which sick persons can be discriminated from not sick according to ESQ criteria. Although formal clinical assessments were not done by a physician, all subjects completed the study and none declined participation in the vigorous daily activities during moderate altitude exposure.

Previous studies have shown the benefit of the use of acetazolamide in preventing the symptoms of AMS at higher altitudes.[6-8,14,15] We found acetazolamide to be effective in reducing the respiratory symptoms of AMS, but it failed to have a statistically significant effect on the cerebral symptoms. In view of the consistent trends, the latter result is likely due to the small size of the study sample.

In a study by Johnson and colleagues, the use of dexamethasone was efficacious in preventing the symptoms of AMS under conditions of simulated high altitude.[5] In our study, dexamethasone use alone did not result in a statistically significant relative risk reduction compared with that of placebo; at moderate altitudes, however, cerebral edema may be so mild that dexamethasone's benefit is hard to measure. Studying the use of dexamethasone at extreme altitudes may prove to be of benefit. It is interesting to note that combined drug therapy led to a significant reduction in the risk of AMS that was nearly equivalent to the additive individual effects of acetazolamide and dexamethasone. This finding is consistent with the biologic model in which acetazolamide primarily works by promoting renal bicarbonate excretion and dexamethasone reduces cerebral blood flow, as suggested by a decrease in retinal artery width associated with its use.[5]

In light of the high incidence but mild nature of AMS among recreational backpackers ascending to moderate altitudes, an argument for drug prophylaxis could be made only if the medications had infrequent, well-tolerated side effects. Our subjects given acetazolamide had a limited number of mild, well-tolerated side effects (Table 1) that have also been noted in other studies.[7,24] In contrast to a previous report,[5] in our study dexamethasone use was associated with a wide array of side effects, including pronounced fatigue, weakness, depression, irritability, and light-headedness for up to 24 hours after the study conclusion. In fact, our side effect survey was prompted by complaints from those who had received dexamethasone. In the absence of a cosyntropin (Cortrosyn) stimulation test in affected subjects, we speculate that those given dexamethasone had some degree of adrenal insufficiency, judging from their symptom complex.[25] Indeed, Johnson and co-workers showed that morning plasma cortisol levels are substantially suppressed with the dosage of dexamethasone given in our study.[5] Although a week to ten days is generally considered the minimal duration of time necessary to suppress the hypothalamic-pituitary adrenal axis,[26] supraphysiologic doses of dexamethasone along with the hypoxemia of high altitude may render the adrenal gland less responsive over a shorter period of time. In patients receiving metyrapone, abnormalities in the hypothalamic-pituitary axis have been noted as early as three days after the initiation of glucocorticoid therapy.[27]

Because Reno is at an altitude of 1,340 m (4,400 ft), an argument can be made that the low AMS scores were due to prior acclimatization by our study subjects living at this modest elevation. At 1,340 m the partial pressure of dissolved arterial oxygen produces a saturation higher than 90% in healthy persons. Hematologic data obtained before ascent did not show an elevated hematocrit in any person, making the presence of chronic hypoxia unlikely in our study popula-

TABLE 1.—*Side Effects of Drug Therapy**

	Treatment Group			
	Placebo	*Dexamethasone*	*Acetazolamide*	*Dexamethasone and Acetazolamide*
No. Responses/Total in Group:	*8/8*	*8/9*	*6/7*	*8/8*
Responses—Specified	*No. (%)*	*No. (%)*	*No. (%)*	*No. (%)*
Numbness, fingers	0	0	6 (86)	5 (63)
Numbness, face and lips	0	0	2 (29)	4 (50)
Visual disturbances	0	0	2 (29)	0
Distaste to carbonated beverages	0	1 (11)	1 (14)	5 (63)
Excessive urination	0	0	0	4 (50)
Metallic taste	0	0	0	3 (38)
Fatigue after trip	0	7 (78)	0	6 (75)
Depression after trip	0	7 (78)	0	5 (63)
Insomnia after trip	0	5 (56)	0	2 (25)
Heartburn	0	4 (44)	0	4 (50)
Euphoria during trip	0	4 (44)	0	2 (25)
Irritability	0	4 (44)	0	2 (25)
Light-headedness after trip	0	3 (33)	0	2 (25)
Hiccups	0	2 (22)	0	4 (50)
Headache after trip	0	2 (22)	0	2 (25)
Sexual dysfunction	0	2 (22)	0	0
Nausea	0	1 (11)	0	2 (25)
Leg swelling	0	0	0	1 (13)
Responses—Open-ended				
Carbohydrate craving after trip	0	1 (11)	0	0
Leg cramps after trip	0	1 (11)	0	0
Nosebleed after trip	0	0	1 (14)	0
Hot flashes 30 min after drug(s) taken	0	0	0	1 (13)
Decreased urination	0	0	0	1 (13)

*Based on a 94% (30 of 32) response rate. Symptoms were found to cluster under the dexamethasone and acetazolamide groups alone (listed in descending frequency within each group). Symptoms may have occurred either during or after trip, unless specifically stated above.

tion. Indeed, chronic altitude sickness has not been described at an elevation of 4,400 ft.

Considering the mild nature of AMS, routine drug prophylaxis does not seem warranted. In those having a history of AMS[28,29] or planning to ascend rapidly to high altitudes, the use of acetazolamide seems acceptable for its efficacy and safety profile. We do not recommend the use of dexamethasone alone. Although combined drug therapy with acetazolamide and dexamethasone provided the best reduction in the risk of AMS, this treatment should be restricted to those refractory to prophylaxis with acetazolamide. The efficacy of combined acetazolamide-dexamethasone therapy should be further studied during mountaineering expeditions to extreme altitudes. In such instances, consideration should be given to withdrawing dexamethasone therapy gradually over several days to avoid the possibility of adrenal crisis.

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Clinical Medicine

Experience of a Wyoming County Streptococcal Control Project

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Figures from Natrona County, Wyoming, during the period 1957-1959 and from the Papago Indian Health Service in Arizona during the years 1970-1982 indicate that a vigorous control program targeted to school children that used throat culturing to detect group A streptococci and to recommend adequate treatment effectively lowered the incidence of first attacks of rheumatic fever. Statistics from the Wyoming Department of Public Health for the years 1972-1983 recorded a consistently lower rate of rheumatic fever in Natrona County, where such a control program was maintained, than for the rest of the state, although the national decline in rheumatic fever incidence makes these figures more difficult to assess. Experience gained in these programs may be valuable for third world countries where rheumatic heart disease is still a major cause of death and disability.

(Phibbs B, Lundin SR, Watson WB, et al: Experience of a Wyoming county streptococcal control project. West J Med 1988 May; 148:546-550)

Rheumatic heart disease remains the only completely preventable affliction of the heart. While rheumatic fever and rheumatic heart disease have substantially disappeared from affluent western society, a recent outbreak of acute rheumatic fever in Utah is at odds with this trend.[1] These diseases remain major causes of death and disability in third world countries. This can only mean that the available means of prevention are not being applied in these areas. For this reason, the experience gained in primary prevention efforts in the United States when rheumatic heart disease was a significant health problem may well have global application. Because the northern Rocky Mountain region was known as one of the three high-risk areas in the United States, the largest and most sustained primary prevention programs were centered here.

First attacks of rheumatic fever are prevented by detecting and treating cases of streptococcal pharyngitis before the rheumatic process has begun. Treatment is relatively simple, but diagnosis presents problems for several reasons:

- Diagnosing streptococcal pharyngitis definitively is not practicable, since it rests on showing rising antistreptococcal antibody titers over a period of several weeks.[2]
- Diagnosing clinically on the basis of symptoms and signs is impossible: even in the best hands, these are not reliable indices.[3]
- A presumptive diagnosis is the best that current techniques can provide. Such a diagnosis may be assumed when a culture is positive in the presence of any symptoms or signs of pharyngitis, but many such cases will actually represent carrier states.[4]

In the conventional or "practice" setting, preventing first attacks of rheumatic fever would require that every case of streptococcal pharyngitis generate symptoms sufficiently severe to prompt a visit to a physician, that every physician use a throat culture to establish a diagnosis, and that treatment be always adequate. As a matter of practical experience, this chain of events is not the rule.

As Massel and co-workers pointed out,[5] the symptoms of streptococcal pharyngitis preceding documented rheumatic fever are often so mild the victim never brings them to anyone's attention. Simple inquiry reveals that many parents treat pharyngitis by giving aspirin or throat lozenges, and in the 1950s and 1960s, a distressing number of physicians did not know the proper treatment for streptococcal pharyngitis.[6]

In the period 1950-1970, a number of investigators, recognizing these inadequacies in conventional health care delivery, organized programs of mass surveillance and treatment among schoolchildren, the group at highest risk of rheumatic fever. All programs were based on the concept of a liberal use of throat cultures in children with symptoms or signs of pharyngitis, together with vigorous attempts to ensure appropriate treatment.

The first successful sustained large-scale program of this type was organized in 1954 in Casper, Wyoming; the same protocol was later implemented throughout the state. The design of the program was simple: every morning in every schoolroom, teachers asked the children if any had symptoms of a "cold" or sore throat. Those admitting symptoms were directed to a central station where throats were inspected and specimens were taken for cultures. Later experience showed that many children had florid signs of pharyngitis without symptoms. To detect this group, one row from each schoolroom was inspected daily for signs of pharyngeal inflammation. Children having a positive culture in

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Reprints are not available.

the presence of symptoms or signs of pharyngitis were excluded from school until treatment had been started or, in cases where religious convictions precluded treatment, until a culture was reported negative. This exclusion was legally enforceable because streptococcal pharyngitis is a reportable, excludable disease in every public health code.

Similar programs were later organized in Fort Collins, Colorado, by Jackson and colleagues[7]; in the Sangre de Cristo school district of southern Colorado[8]; among Alaskan natives by the streptococcal section, ecological investigations division, Centers for Disease Control (CDC)[9]; and among the Navajo and Papago tribes of Arizona by the University of Arizona Medical Center, Tucson.[10] The protocols in all were in essence the same, based on an aggressive search for streptococcal infection in schoolchildren populations, with a maximal effort to treat those found to be infected.

Methods

The laboratory methods used in all projects were essentially the same, with incubation of sheep's blood agar in a carbon dioxide-enriched, semianaerobic atmosphere. Grouping was carried out initially by the weak-bacitracin-disc method and later by an immunofluorescent-antibody technique. In the Casper program, school nurses initially did the throat swabbing; later, a large number of mothers were recruited from Parents and Teachers Associations and trained in physicians' offices in the techniques of inspecting the pharynx and obtaining a specimen for throat culturing. This was the first widespread use of paramedical personnel in the United States and it proved very successful. Not only did the volunteers acquire professional levels of skill in inspecting and swabbing the pharynx, but the educational effect of this training throughout the community was a major benefit of the program. In the CDC programs, both professional and volunteer help was used in obtaining specimens for throat cultures. Standard American Heart Association recommendations for treatment were followed throughout. In the Casper program, treatment was legally required; in others, it was strongly urged, resulting in a high level of compliance.

Results

The results of such programs may be assessed on the bases of their effect on the incidences of streptococcal infection and of new cases of rheumatic fever.

The Level of Streptococcal Infection

The effect of the programs on the incidence of streptococcal infection can be evaluated in three ways:

- Documenting streptococcal isolation rates compared with those of a control group.
- Studying antistreptococcal antibody titers compared with those of a control group.
- Studying streptococcal isolation rates throughout the period of surveillance as compared with the expected seasonal levels established by studies in schoolchildren.

The Casper program was started in 1954 and by 1957 had expanded to include all Natrona County schools. By 1960 considerable experience had been accumulated, techniques had been standardized, and the laboratory had improved performance with the assistance of staff from the University of Colorado Medical Center.

In 1964 the Centers for Disease Control group set up epidemiologic studies in two Colorado communities to establish streptococcal prevalence rates. By 1969 consistent patterns in terms of isolation rates and antibody profiles had been recorded; thus, a "control" group was available.

In 1965 the CDC group visited Natrona County on two occasions during the school year, obtaining throat specimens for culture and blood specimens for antibody study from randomly selected groups of schoolchildren. The results of this study proved that the surveillance and treatment program had had a dramatic effect on levels of streptococcal infection. The isolation rate of 1.3% recorded by the CDC workers was the lowest ever recorded in a temperate-zone schoolchildren population,[11] contrasting strikingly with the levels of 15% to 30% recorded during the same period in the Colorado schoolchildren. Continuing comparison of isolation rates throughout the school year with frequent cross-checks of cultures in the two laboratories to ensure comparable results showed an isolation rate in the Colorado children fivefold to sixfold the level in the Casper children at all times (Figure 1). In addition, antibody profiles showed a very low level of current and antecedent infection in the Casper children as compared with the Colorado schoolchildren.

Subsequently, the CDC group instituted a similar program in the Sangre de Cristo school district of southern Colorado, with a reduction of prevalence rates to 4.5% as compared with levels of 21.9% recorded by the same group in other Colorado communities (Figure 2). A substantial "carryover" effect was recorded with lower levels of isolation rates in children at the beginning of the second year of the study.[8] Zimmerman and CDC associates were able to reproduce these results in Alaskan native villages, even under the handicap of remoteness from laboratory facilities and serious logistic problems.[9] Jackson implemented surveillance-treatment programs in schoolchildren in Morgan

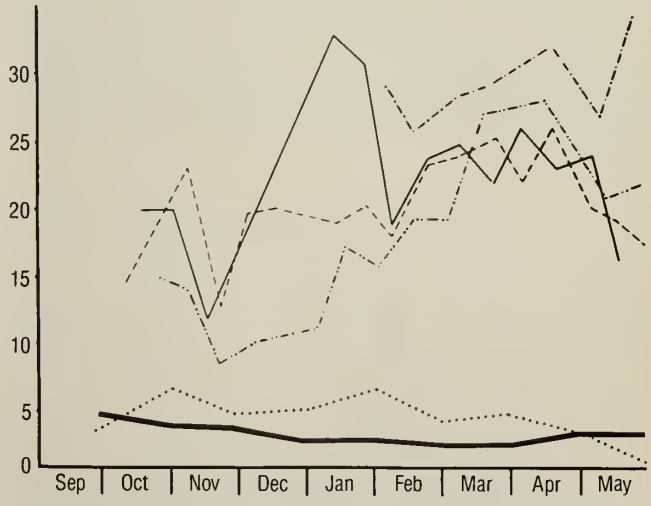

Figure 1.—Streptococcal isolation rates in Casper-Natrona County, Wyoming, schoolchildren during school years 1964-1965 and 1965-1966 compared with rates in children in three Colorado communities.

— = Frisco, Colo, 1965-1966
-·-·-·- = Loveland, Colo, 1965-1966
—·—·— = Colorado Springs, Colo, 1964-1965
- - - - = Colorado Springs, Colo, 1965-1966
····· = Natrona County, 1964-1965
▬ = Natrona County, 1965-1966

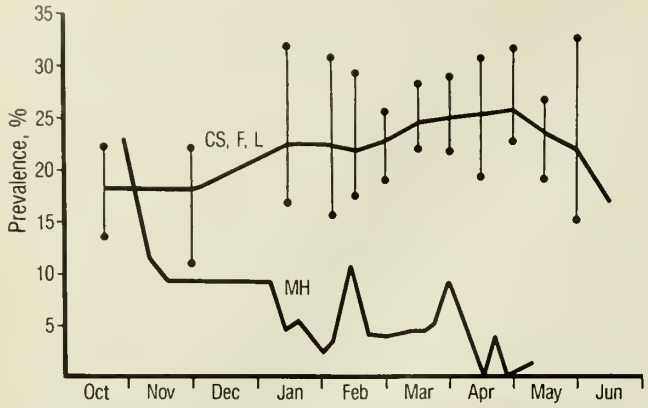

Figure 2.—The rates of prevalence of group A *Streptococcus* in Mosca-Hooper, Colorado (MH), 1969-1970, are compared with those in Colorado Springs, Frisco, and Loveland, Colorado (CS, F, and L). The vertical lines represent minimum and maximum prevalence rates (from Zimmerman et al,[8] reproduced by permission).

County, Colorado, and compared the efficacy of several protocols.[7] He found that when a rigid protocol was applied, organism identification rates fell as low as 6.9% as compared with control levels of 21.9%. With the assistance of the University of Arizona, in 1973 the Disease Control Program of the Papago tribe organized an intensive program of streptococcal surveillance and treatment involving all tribe members. The results, published in 1982,[10] included a drop in identification rates in schoolchildren from 9.3% in 1973-1974 to a consistently low level in the years 1978-1980, with yearly averages ranging from 2.2% to 3.8% (Figure 3). The same carryover effect noted by the CDC workers was recorded in the Papago study, with lower levels in schoolchildren at the beginning of each succeeding year.

Seasonal patterns of streptococcal identification rates have been documented in a number of studies. Almost without exception, the rate rises sharply during the first months of school and persists at a high level through the school year.[12] In all the programs, this profile was altered with a sharp drop in rates of identifying the organisms after the initial rise in the fall months and with sustained low rates throughout the school year. A rise after the winter holidays was a common observation, with a subsequent drop to the lower levels.

It appears that intensive surveillance and treatment programs can alter the "total streptococcal milieu" in a favorable manner. Even a loosely organized project by Hubbard and co-workers produced a significant fall in identification rates in Philadelphia schoolchildren. These workers failed to recognize the significance of their own results and fell into the trap of trying to differentiate carrier states from active infections by the appearance of the pharynx, a notion refuted by their own subsequent antibody studies.[13]

Occurrence of New Cases of Rheumatic Fever

The effect of the programs on the occurrence of first attacks of rheumatic fever is much more difficult to record for several reasons. First, reporting by physicians to public health authorities is notoriously poor. In Colorado investigators found that only 15% to 20% of cases were being reported to the state.[14] Overdiagnosis and errors in diagnosis are common.[15] Second, as often as not, rheumatic fever is insidious; streptococcal infections are followed by rheumatic heart disease without overt clinical rheumatic fever in about 50% of all cases.[16] With these limitations in mind, the following estimates can be made:

- In Natrona County, the Asian influenza epidemic of 1957 was followed by recurrent epicenters of streptococcal infection that erupted for almost two years. At that time the school surveillance program was in effect, but the culture and treatment facilities had not involved the remainder of the population. The streptococcal epidemic was followed by an epidemic of acute rheumatic fever that persisted with remissions and exacerbations until the end of the 1959 school year. In a three-year period there were 25 new cases of acute rheumatic fever among the non-schoolchildren population of the county; among the schoolchildren, there were 4.* The significance of this difference is heightened by the fact that in normal circumstances, 85% of new cases of rheumatic fever occur in schoolchildren during the school year.[17]

- The Papago tribe of Arizona is a closely knit ethnic group of 13,000 living in a remote desert area. Nothing in the style of living of the tribe changed in the years 1973 to 1980,

*Source: Records Department, Natrona County Memorial Hospital, Casper, Wyoming. All cases were reviewed and verified by the Rheumatic Fever Committee of the Natrona County Medical Society.

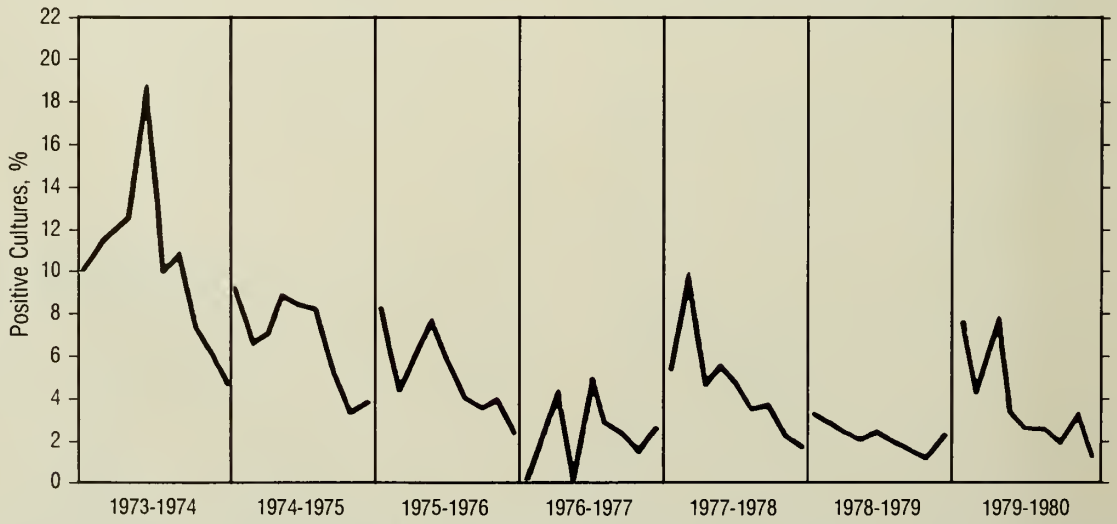

Figure 3.—The graphs show the percentage of positive cultures found during streptococcal screening in schools in the academic years, September to May, 1973-1980 (from Atha et al,[10] reproduced by permission).

TABLE 1.—*Streptococcal Organisms Identified in Throat Cultures by Monthly Averages and Positivity, Casper-Natrona County Streptococcal Control Project, 1963-1964 Through 1982-1983 School Years*

	Monthly Averages								
	Sep	*Oct*	*Nov*	*Dec*	*Jan*	*Feb*	*Mar*	*Apr*	*May*
Average positive cultures, No. . .	292	611	570	360	616	446	422	342	172
Average cultures, No.	4,173	10,064	9,598	7,005	11,596	10,393	10,630	9,156	5,276
Percent positive	7.0	6.1	5.9	5.1	5.3	4.3	4.0	3.7	3.3

and the only change in health care delivery was the institution of the surveillance program. The fall in the number of new cases of rheumatic fever to 0 in 1978 from the high of 12 in 1970 and the previous six-year average of 6 per year may therefore reasonably be attributed to the control program.

• Gordis recorded a significant fall in the incidence of new cases of rheumatic fever when intensive medical management was introduced to inner-city populations in Baltimore.[18] This program included intensive surveillance and treatment projects directed at schoolchildren.

Wyoming Statistics for the Period 1973-1982

Because the Wyoming control program was the only project that applied the surveillance measures described above to an entire state, the statistics available to the state health department are of some interest. Identification rates recorded by hundreds of workers in different communities cannot be compared, since they probably reflect the enthusiasm or discrimination of the various workers as much as a difference in prevalence. The total percentage, however, of positive cultures by months between the years 1963-1964 and 1982-1983 confirms the reversal of the expected seasonal fluctuation of streptococcal prevalence, with a consistent fall in rates throughout the school year and overall levels below any recorded control group (Table 1).

A regression analysis between years and number of reported cases of rheumatic fever per 100,000 population was carried out for Casper-Natrona County and for the rest of the state of Wyoming outside Natrona County. Over a ten-year period of the Rheumatic Fever Registry (1973-1982), the incidence of rheumatic fever declined statistically for both Casper-Natrona County ($f[1,8] = 5.98$, $P = .0402$) and the rest of Wyoming ($f[1,8] = 46.62$, $P < .0001$). A natural log transformation was done to take into account the curvilinear nature of the declining rate in rheumatic fever incidence. During this ten-year period, an average of 1.7 cases of rheumatic fever was reported per 100,000 population per year for Casper-Natrona County. The rest of Wyoming, however, reported an average of 6.4 cases per 100,000 population per year for the same period.

The incidence of rheumatic fever was consistently lower for Casper-Natrona County than for the rest of Wyoming during this ten-year period. There were no reports of rheumatic fever for Casper-Natrona County for 1980, 1981, and 1982. By 1982, the incidence for the rest of Wyoming was only 0.7 cases per 100,000 population (Figure 4). (Through 1985, the incidence of acute rheumatic fever has stabilized at zero for Casper-Natrona County while three to four cases per year were reported for the rest of Wyoming [case rate 0.7 to 1.0 per 100,000 population per year].) The nationwide decline in the occurrence of rheumatic fever through this same period and the unreliability of reporting by physicians make these figures more difficult to assess, but the difference between Casper-Natrona County and the rest of the state appears significant.

Discussion

The results produced by a number of different investigators confirm the possibility of altering the total streptococcal milieu in a favorable manner by programs of intensive surveillance and treatment. The near disappearance of acute rheumatic fever from the affluent western world while the disease persists in a virulent form and at high levels among underserved populations speaks strongly for the effectiveness of modern diagnosis and treatment and for applying these techniques, in some manner, to populations at risk. The extremes of poverty in many parts of the globe make it unlikely that the private practice paradigm of western medicine will be available for a long time, if ever. Organized programs of control such as those described here may play an important role in certain specific settings.

Prompt diagnosis and treatment may also help to account for the diminished virulence of the streptococcus in western society through diminished opportunities for animal passage.

The Natrona County, CDC, and Morgan County projects all discovered and documented the importance of surveillance by inspection or culturing of a significant number of the asymptomatic children in any organized control program. The common occurrence of signs of pharyngeal inflammation without symptoms came as a surprise to the workers in all projects.

Without question, the educational impact of such programs is a major benefit. When parents are familiar with the

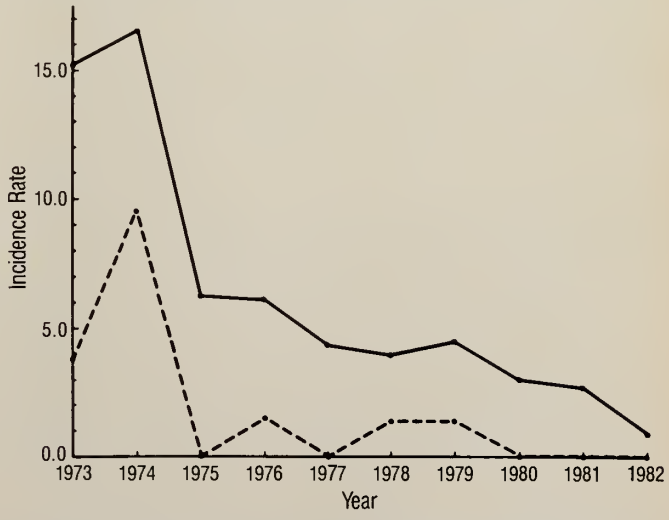

Figure 4.—The graph shows reported cases of rheumatic fever per 100,000 population for Wyoming and Casper-Natrona County, 1973-1982. -·-·- = state of Wyoming without Casper-Natrona County, ---- = Casper-Natrona County

sequelae of streptococcal infection and when they are prepared to insist on adequate diagnosis and treatment, the conquest of rheumatic fever is simply a matter of time, financing, and medical logistics.

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Clinical Review

Post-Lumbar Puncture Headache

Etiology and Management

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Headache following a lumbar puncture is a common and often debilitating syndrome. Continued leakage of cerebrospinal fluid from a puncture site decreases intracranial pressure, which leads to traction on pain-sensitive intracranial structures. The headache is characteristically postural, often associated with nausea and optic, vestibular, or otic symptoms. Although usually self-limited after a few days, severe postural pain can incapacitate the patient. Management is mainly symptomatic, but definitive treatment with the epidural blood patching technique is safe and effective when done by an expert operator.

(Raymond JR, Raymond PA: Post-lumbar puncture headache—Etiology and management. West J Med 1988 May; 148:551-554)

Headache following a lumbar puncture is a common and sometimes incapacitating syndrome that has been recognized for approximately 100 years. August Bier, the father of spinal anesthesia, is generally credited with reporting the first instance in 1899; he was also the patient.[1] Corning, however, was possibly the first to document, albeit vaguely, post-lumbar puncture headache in a patient he had treated in 1885 with the dural or epidural administration of cocaine for a sexual disorder.[2] Post-lumbar puncture headache continues to be a problem to this day, although suggested treatments abound. In this article we review the characteristics, pathogenesis, precipitating factors, and possible treatments.

Report of a Case

A 29-year-old man with a history of unrepaired anal fistula presented with a complaint of perianal firmness for two weeks, 12 hours of rectal tenderness, and a temperature of 38.9°C (102°F). The findings of an examination were consistent with perirectal abscess, and the patient was prepared for operation. With the patient under spinal anesthesia using a 25-gauge needle and a single puncture, uneventful incision, drainage, and fistula repair were done. The patient's temperature became normal without administration of antibiotics, and he was discharged after 12 hours of recumbency. He attempted to return to work later that day but was foiled by the development of an excruciating fronto-occipital postural headache and nausea. The results of a neurologic examination were normal, and a diagnosis of post-lumbar puncture headache was made. Bed rest (except for sitz baths), salicylates, and hydration with 2 to 3 liters by mouth per day were prescribed. Despite strict adherence to the prescribed regimen, the headache worsened over the next two days to the point where the patient could barely lift his head off a pillow. Acetaminophen and codeine were prescribed, yielding minor relief. Neck ache and tinnitus developed over the next day. After six days in bed, the patient was readmitted to hospital for an epidural blood patch. The results of a neurologic examination were still normal, as were pulse rate and blood pressure levels. Membranes were moist and there was no orthostasis. The patient was taken to a recovery room where 15 ml of his blood was removed aseptically from the antecubital fossa and injected into the epidural space at L-3, over the previous lumbar puncture site. Almost instantaneous relief resulted. The patient was hydrated with 1 liter of lactated Ringer's solution, and he rested supine for one hour. He left the hospital virtually pain-free, and no ill effects of the procedure and no relapse were noted.

Characteristics of Post-Lumbar Puncture Headache

This case illustrates some of the typical features of post-lumbar puncture headache. The headache, which can begin within hours, typically starts 24 to 48 hours after a dural puncture. It is usually frontal or occipital and often radiates to the nuchal area and behind the eyes. It is postural, most severe when the patient is upright, and subsides when the patient is recumbent. Occasionally, nausea or diplopia may occur.[3] The headache is usually self-limited, resolving within days to weeks (mean duration four days). These characteristics should be kept in mind when evaluating a patient with headache after a dural puncture, so as not to miss subdural hematoma, subarachnoid hemorrhage, preeclampsia, or other possible causes of headache. This patient's symptoms, normal neurologic findings, and course are most consistent with post-lumbar puncture headache.

Pathogenesis

Bier initially suggested that persistent cerebrospinal fluid (CSF) leaking through the dural puncture site caused the headache—a result of decreased intracranial pressure.[1] Wolff subsequently showed that removal of CSF from subjects in the sitting position resulted in a decrease in intradural pressure.[4] Repeated removal resulted in a headache that could be relieved by having the patient recline or by reinjecting the CSF. Cerebrospinal fluid leak after a dural puncture has been shown by direct visualization and by radioisotope myelography.[5,6]

Headache following a lumbar puncture is thought to be

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due to a downward shift of the brain relative to the dura, with subsequent stretching of pain-sensitive structures such as blood vessels, nerves, and dura. Compensatory dilation of intracranial blood vessels may also play a role in its genesis, as the headache may be increased by compressing the jugular veins. Symptoms may be due to stretching of specific nerves. The second and third divisions of the trigeminal nerve above the cerebellar tentorium transmit frontal pain; and the glossopharyngeal, vagus, and upper three cranial nerves below the cerebellar tentorium transmit neck and suboccipital pain.[4,7,8] Diplopia may be due to stretching of the abducens nerve where it crosses the petrous portion of the temporal bone.[9] Tinnitus, vertigo, and ataxia may be caused by decreased amounts of endolymph because semicircular and cochlear canals are in communication with the cerebrospinal fluid.[3]

Precipitating Factors

The incidence, duration, and severity of post-lumbar puncture headache are influenced by several factors, including the magnitude and rapidity of the CSF leak, the rate of formation of CSF, and the length of time required to repair the dural leak. Normally, approximately 20 ml per hour of cerebrospinal fluid is produced by the choroid plexus to maintain a total CSF volume of 140 to 170 ml.[10] After a single puncture with a 20-gauge needle, a CSF leak averages about 10 ml per hour.[11] Because the dural tear typically takes many days to heal, there may be a considerable net loss of CSF. The amount of fluid lost depends primarily on the number and size of dural punctures.

Several factors determine the amount of CSF leak, including needle size, design of the needle tip, number of punctures, and angle of the needle insertion. The data in Figure 1 illustrate the relationship of needle size to incidence of headache in ten series.[12-21] Our case is somewhat unusual in that a single puncture with a 25-gauge needle is associated with only a 1% incidence.[15,16] The design and angle of insertion of the needle tip also influence the incidence of post-lumbar puncture headache. Needles that separate rather than transect the longitudinal dural fibers produce smaller holes than the typical beveled needle.[14,22,23] The size of the dural tear can also be decreased by inserting the needle with the bevel parallel to the longitudinal dural fibers.[24] The angle of the needle insertion may also affect the volume of the CSF leak. A tangential puncture seems to create less leakage than a perpendicular puncture, possibly because the separate arachnoid and dural punctures slide over each other and seal the leak.[25]

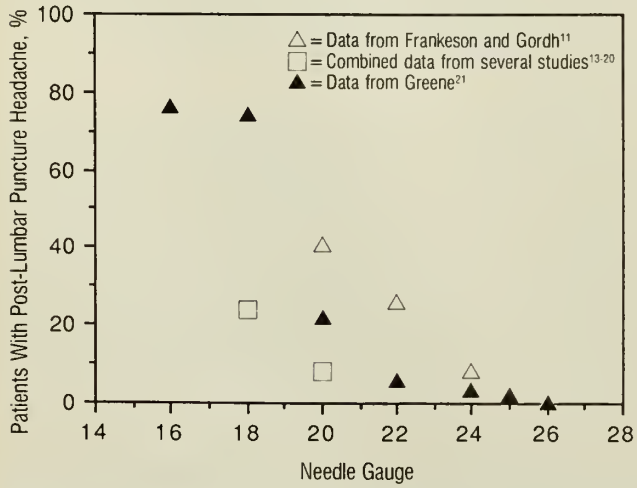

Figure 1.—The effect of needle size on post-lumbar puncture headache is shown.

Age may be an important factor in the development of headache following a lumbar puncture. Young adults seem more susceptible than children younger than 10 years or adults older than 60. In one series, patients aged 20 to 29 had a fourfold greater incidence than patients aged 60 to 69.[3] This effect may be secondary to decreased elasticity of pain-sensitive intracranial structures, decreased sensitivity to pain, or structural or mechanical changes in the epidural space with age. The incidence also appears to be higher in women.[3] It has been suggested that this sex difference is due to the high number of parturient women included in the data analysis.[26] In studies excluding parturients, however, women still have a higher incidence.[27,28] This is thought to be multifactorial, but the implicated factors have not been convincingly shown to be causative. These include dehydration and blood loss, hormonal effects, stress, and the Valsalva maneuver during "bearing down."[26] It is commonly thought that dehydration due to blood loss, diaphoresis, and withholding of fluids exacerbates post-lumbar puncture headache. This has never been proved with a randomized trial, although dehydration decreases CSF production. The role of maternal bearing down has also been disputed.[29] Psychological factors have been implicated in the genesis of post-lumbar puncture headache[30-32]; however, psychogenic factors are certainly minor compared to the mechanical features previously discussed.

Prevention

The most important factor in the prevention of post-lumbar puncture headache clearly is the size of the dural puncture site. The preventive role of posture and bed rest is less clear. Routinely, 24 hours of bed rest is prescribed after a lumbar puncture to decrease the hydrostatic pressure on the dural puncture site. This maneuver theoretically decreases the rate of cerebrospinal fluid leak and accelerates healing. Severe post-lumbar puncture headache developed in the patient in our case study despite 12 hours of bed rest in a supine position.

In 1902, Sicard first discussed the benefit of 24 hours of bed rest after lumbar puncture.[33] Despite common use, postural maneuvers and bed rest are not of proved merit in preventing post-lumbar puncture headache. Two groups have suggested that bed rest only delays its onset but does not alter the incidence or duration of the headache.[27,34] Other groups have advocated the prone[35] or lateral[36] positions, but their results have not been duplicated.[28,37,38] Bed rest seems to be of little value in preventing the headache but reduces its severity.

The prophylactic use of the epidural blood patch technique is somewhat effective in preventing post-lumbar puncture headache,[40,41] but the success rate is much lower within the first 24 hours after lumbar puncture.[42] Gormley first described the successful use of the epidural blood patch in 1962.[43] Autologous blood is injected into the epidural space, coagulating and sealing the dural leak. This is an effective treatment, but its prophylactic use generally is not recommended due to the usually self-limiting nature of the headache.

Treatment

Although more than half of post-lumbar puncture headaches last less than four days and 75% resolve within seven days with conservative management,[3] the debilitating nature of the symptoms often requires aggressive management. Most measures address the mechanical causes of the headache, although analgesia and psychological interventions also play an important role. The patient presented in our review was managed in the usual manner, proceeding from conservative to more aggressive measures. Bed rest, hydration, and progressive analgesia were followed by reassurance and finally by an epidural blood patch. Bed rest, where CSF pressures are nearly equal in the lumbar area and cisterns, yields relief by minimizing the effects of gravity on pain-sensitive intracranial structures. Bed rest merely reduces the symptoms but probably does not speed recovery.[33] Analgesia plays a major role in the management of post-lumbar puncture headache. Mild analgesics—acetaminophen, ibuprofen, the salicylates—should be used first, with escalation to narcotic agents as needed.

Hydration is universally advocated in the treatment of post-lumbar puncture headache, although controlled studies have not been done. Theoretically, adequate hydration ensures a ready pool of fluid for the manufacture of CSF. Pharmacologic antidiuresis with the administration of desmopressin acetate or vasopressin tannate may have limited usefulness,[44,45] although oral or intravenous hydration is safer and more easily titrated. Other pharmacologic treatments such as intravenously given ethanol,[46] nicotinic acid,[14] theophylline,[47] and caffeine,[48] or inhaled carbon dioxide[49] are of uncertain merit.

Efforts to increase the epidural pressure with abdominal binders[50,51] and epidural saline infusions or boluses[19,20,52] provide relief but their use is cumbersome.

The epidural blood patch is clearly the most effective therapy for persistent post-lumbar puncture headache, with at least a 90% success rate.[53-55] The technique is as follows: an epidural tap is done at the level of the previous lumbar puncture. A small amount (10 to 20 ml) of the patient's own blood is aseptically drawn into a syringe and slowly injected into the epidural space. The injection is slowed or discontinued if back pain develops and discontinued if paresthesias develop. Concomitant intravenous hydration is administered while the patient lies supine for an hour. Relief is usually instantaneous. The initial relief is due to the prompt elevation of the CSF pressure. Lasting relief is probably due to stopping the CSF leak. Most failures are thought to be due to injecting an inadequate amount of blood, an incorrect diagnosis, or not injecting blood into the epidural space.[54] Often, a second epidural blood patch will be successful.[51] The relative risks are low. Residual back stiffness may occur in up to 15% of patients but resolves within one day to three months.[55] Transient paresthesias and painful radiculopathy have also been reported.[55,56] Subdural hematoma is a rare complication associated with multiple puncture attempts.[57] Another potential concern is the possible restricted spread of analgesia with subsequent epidural anesthesia.[48,58,59] Other potential complications such as adhesive arachnoiditis and bacterial meningitis have not been reported.

Although the relative risks of the epidural blood patch are low, several precautions should be employed. The procedure should be limited to patients with debilitating headache refractory to conservative management. It should be done by or under the close supervision of an expert operator. Strict asepsis should be maintained. Blood should be injected no more rapidly than 1 to 2 ml every 10 seconds. The procedure should be terminated if paresthesias develop and slowed or terminated if back or neck pain occurs during the injection.

Differential Diagnosis

Although most headaches after lumbar puncture are due to CSF leak, one must carefully examine the patient, with particular attention to blood pressure levels and the results of funduscopic and neurologic examinations. The history and characteristics of the headache should be consistent with a diagnosis of post-lumbar puncture headache. If the headache is not postural, one should consider other causes such as pre-eclampsia or eclampsia,[60] cerebrovascular accident,[61] subdural hematoma,[62] intracranial hemorrhage,[63] or meningitis.

Summary

Headaches commonly occur after a lumbar dural puncture. The great majority are due to cerebrospinal fluid seepage from the puncture site, with subsequent traction on pain-sensitive intracranial structures. Characteristically, the headache is postural, often associated with nausea and optic, otic, and vestibular symptoms. The headache is usually self-limited after a few days. If the headache is not postural or if the neurologic findings change, other causes must be considered. The only effective means of preventing post-lumbar puncture headache is to use the smallest possible needle and the fewest possible dural punctures. The initial steps in managing the headache include bed rest to reduce the severity of the headache, analgesia, hydration, and reassurance. If a debilitating headache persists, epidural blood patching is a safe, effective treatment that usually offers nearly instantaneous relief. When needed, a second blood patch is effective. To minimize possible complications, epidural patching should be done only by physicians thoroughly trained in the procedure.

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Specialty Conference

'Ruling Out' Myocardial Infarction in the Coronary Care Unit

Discussant
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This discussion was selected from the weekly Grand Rounds in the Department of Medicine, University of New Mexico School of Medicine, Albuquerque. Taken from a transcription, it has been edited by Ralph C. Williams, Jr, MD, Professor and Chair of the Department of Medicine.

GLEN H. MURATA, MD*: Although many advances have been made in the treatment of myocardial infarction (MI), cardiovascular disease is still the most common cause of death for adults in the United States. Each year, 1.5 million Americans have a heart attack, and a third of them die. Most of these deaths occur soon after the onset of symptoms and are caused by ventricular fibrillation.[1] Because this arrhythmia responds promptly to cardioversion and the use of lidocaine in the absence of severe ventricular dysfunction,[2] patients with an acute MI should be admitted to a hospital setting where these interventions are readily available. It has also become customary for patients with chest pain to be monitored in a coronary care unit (CCU) until a diagnosis can be made. As a result, more patients in CCUs have the diagnosis of myocardial infarction "ruled out" than confirmed.[3-7]

Although coronary care units are widely used in the United States,[8] their value for patients with myocardial infarction has been controversial.[9-17] The best studies on this subject have failed to show that such care reduces short-term mortality.[18-20] Moreover, there is not a single randomized study to show that coronary care reduces mortality for patients with chest pain while their workup is in progress. Thus, the coronary care unit is an example of a technologic innovation that became widely used before the question of its efficacy could be resolved. Because coronary care is an expensive intervention in an era of rising medical costs, it is reasonable to review the practice of ruling out an MI in the coronary care unit.

I would illustrate the nature of this controversy by posing a difficult but common clinical problem. Suppose that you were working in an emergency department and were asked to evaluate a patient with chest pain. If the patient's risk of myocardial infarction were 5%, would you send the patient home? Before you make a decision, let us examine the cost of admitting this patient.

In 1984 Fineberg and associates[21] analyzed the cost-effectiveness of admitting patients with a low probability of myocardial infarction to a coronary care unit. Their analysis was based on a hypothetical group of 2 million patients with chest pain, of whom 100,000 had an acute myocardial infarction. The authors used what they considered to be the best available data on the effect of coronary care on mortality from primary ventricular fibrillation and heart block. They assumed that other complications of myocardial infarction such as shock, congestive heart failure, and pericarditis occur after the diagnosis is made. These complications would, therefore, have the same outcome regardless of the initial management strategy. Costs were based on charges incurred by patients in the coronary care unit at Brigham and Women's Hospital in Boston in 1980.

For patients with a 5% probability of myocardial infarction, these authors found that admission to a coronary care unit would cost $1,260,000 per life saved and $113,000 per year of life saved compared to home care with outpatient follow-up. Thus, we are faced with a dilemma. We may feel uneasy about sending these patients home; however, it is not cost-effective to admit all of them to hospital. We obviously need a strategy for evaluating these patients that does not compromise their care and is more affordable than a conventional admission to a coronary care unit. This strategy will be the focus of this discussion.

I will first review some historical aspects of coronary care in the United States and try to assess its effect on short-term survival in myocardial infarction and on the overall mortality from cardiovascular disease. I will then describe alternative strategies for evaluating patients who present to an emergency department with chest pain.

Historical Features

Coronary artery disease is an affliction of modern-day living. Its incidence and mortality rate have been dramatically influenced by the life-style, risk factors, and medical interventions of the 20th century. The coronary arteries were first described with accuracy by the French anatomist Raymond Vieussens in 1705. In a report published in 1759, Edward Hyde described symptoms suffered by his father that were consistent with coronary ischemia. The term angina pectoris is credited to William Heberden who provided the first accurate description of the syndrome in 1768. The diag-

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ABBREVIATIONS USED IN TEXT

CCU = coronary care unit
ECG = electrocardiogram
MI = myocardial infarction

nosis of coronary thrombosis was first made in a living patient by the Austrian physician, Adam Hammer, in 1878. It was not until 1912 that a classic description of the clinical features of coronary thrombosis was provided by the American physician, James Bryan Herrick. Thus, myocardial infarction has been a recognized clinical disorder for only 75 years.

Between 1940 and 1967, the age-adjusted mortality rate from coronary artery disease in the United States increased by 14.1% for persons between the ages of 35 and 74.[22,23] Since 1968, however, coronary mortality has fallen by almost 40%. This trend has been noted in men and women of all ages and races and has involved both categories of coronary heart disease—acute myocardial infarction and chronic ischemic heart disease. The decrease in mortality in the former category has been the more prominent.

Coronary care units were first introduced in the United States and Canada in 1962. The first reports of success with these units appeared in the literature in 1963.[24,25] Although Day[24] described a drop in the MI case-fatality rate from 39% to 19% after the opening of a coronary care unit, Brown and associates[25] simply reported an in-hospital mortality of 36%. Over the next 20 years, there was a dramatic increase in both the number of coronary care units and the number of beds. By 1981, hospitals responding to the annual survey of the American Hospital Association[26(p197)] reported 1,960 units and 15,793 beds devoted to the care of patients with cardiovascular disease. Since that time, however, there has been a steady decline in the number of cardiac beds. Although the number of hospitals reporting to the American Hospital Association had not changed appreciably by 1985, the number of cardiac beds had dropped to 13,080.

There is one obvious question that arises from these observations. Can the decline in mortality from ischemic heart disease be attributed to the use of coronary care units for patients with myocardial infarction?

Effect of Coronary Care on Short-Term Mortality in Myocardial Infarction

Before we review the "evidence" that coronary care units have reduced the short-term mortality from acute myocardial infarction, we should define the characteristics of a good clinical study on the benefits of coronary care.

- The study should be prospective in design because this feature allows standards to be set for the diagnosis of myocardial infarction and the intensity of follow-up. Even with laboratory support, it can be difficult to make the diagnosis of myocardial infarction with certainty.[27] Thus, differences in mortality rates between patients given conventional care and those given coronary care could be because of differences in the manner in which the diagnosis is made.
- The use of ancillary modalities should be specified. Mortality from myocardial infarction can be influenced by interventions that do not require electrocardiographic monitoring. These include the use of β-blockers, lidocaine prophylaxis, anticoagulation, and nitrate therapy.
- A good CCU study should specify the time of entry relative to the onset of symptoms. The risk of ventricular fibrillation and heart block is highest immediately after the start of symptoms and declines exponentially thereafter.[1] Different results between two study groups may simply reflect a delay in the transportation or triage of one group.
- A study on the benefits of coronary care should have parallel controls. We have seen that the mortality rate from coronary artery disease has decreased dramatically since 1968. The improved survival of patients in a coronary care unit relative to historical controls may reflect this trend even if coronary care is of no value.
- Ideally, a trial comparing coronary care with conventional therapy should involve randomly assigning patients to the different treatment groups. This process should eliminate bias on the part of a physician who might have strong feelings about the use of a coronary care unit for different types of patients.
- The analysis should be stratified with respect to risk factors. The mortality from myocardial infarction can be influenced substantially by risk factors such as a patient's age and sex; the location and size of the infarct; and the presence of hypotension, heart failure, or a conduction defect.

Dozens of studies in the medical literature have addressed the benefits of coronary care for patients with myocardial infarction. It is beyond the scope of this article to review them all. Almost all, however, suffer from a lack of one or more features that we considered essential for a valid conclusion. For example, many studies used only historical controls or no controls at all, and only two studies in the literature are randomized.[18-20] I think, however, that it is useful to review the best evidence for and against the use of coronary care for patients with myocardial infarction.

Two Scandinavian studies showed that short-term survival is increased by admitting patients with acute myocardial infarction to a coronary care unit.[28,29] Hofvendahl[28] studied 523 patients with presumed myocardial infarction who were assigned to a coronary care unit or a medical ward on the basis of bed availability. Of 250 CCU patients, 53% were eventually diagnosed with myocardial infarction, while 51% of 273 ward patients were given such a diagnosis. The in-hospital mortality of coronary care unit patients with infarction (17%) was significantly less than the mortality of ward patients (35%). No differences were noted between the treatment groups with respect to patient age or sex, time elapsed since the onset of symptoms, history of coronary artery disease, presence of diabetes and hypertension, or signs of ventricular dysfunction on admission. Although this study was not randomized, the difference in outcome between the two treatment groups did not result from an obvious bias in favor of the coronary care unit.

Perhaps the most convincing study on the benefits of coronary care was published by Christiansen and associates in 1971.[29] They studied 812 patients with possible MI who were assigned to a coronary care unit or medical ward on the basis of bed availability. About half of each treatment group was eventually given the diagnosis of myocardial infarction. The 28-day mortality for 171 MI patients in the coronary care unit (18%) was significantly lower than the mortality for 244 MI patients assigned to the wards (41%). The CCU patients had a shorter duration of symptoms and a higher proportion of anterior infarctions than control patients. They were also more likely to present with congestive heart failure. Because the distribution of risk factors should have

favored survival on the wards, the benefits of coronary care were large.

The only randomized studies on coronary care have not shown improved survival for patients with myocardial infarction.[18-20] In two papers, Mather and colleagues reported the results of a randomized study of home versus hospital care for British men younger than 70 years.[18,19] Patients were excluded from the study if they had their myocardial infarctions at work or in hospital, had unfavorable social circumstances, expressed a strong desire for either care option, or had a medical problem requiring hospital care. Of 1,895 episodes of definite or probable MI, only 450 (24%) were randomized. The home and hospital treatment groups were similar with respect to age, history of cardiovascular disease, and incidence of hypotension at entry. At four weeks, the mortality for hospital patients (14%) was no different from the mortality for patients who stayed at home (12%). The final analysis at 330 days showed a statistically significant difference in favor of home care for patients older than 59 years without initial hypotension.

Although this study included randomization, stratifying patients by risk, and some tabulation by each study center, it suffered from the fact that so many patients were excluded from the study. Moreover, only 47% of patients were randomly assigned to care within three hours of the onset of symptoms. As a result, most patients were not in hospital during the period of greatest risk for fatal arrhythmias.[1] It is therefore not surprising that coronary care had no effect on outcome.

Because of these problems, Hill and co-workers[20] conducted another study comparing home versus hospital treatment for patients with possible MI. In the famous Nottingham trial, a hospital team was sent to patients' homes in response to calls from physicians in the community. Of 500 calls, 349 patients were thought to have had a myocardial infarction. Of those, 24% were then excluded because of medical or social problems, and the remainder were randomly assigned to hospital or home care. No differences were noted between the two groups with respect to age, history of previous infarction or angina, or the results of an entry electrocardiogram. Of the home patients, 60% were given the diagnosis of MI, as were 54% of the hospital patients. The six-week mortality for the 132 patients randomly assigned to hospital care (11%) was no different from the mortality for the 132 patients who stayed at home (13%).

Unfortunately, the Nottingham trial did not resolve the problems of the Mather study. Although a higher rate of randomization was obtained, it has been estimated that the Nottingham trial involved only 12% of the cases of MI that occurred in the community.[12] Moreover, the mean time required for randomization was five hours. The patients in this trial were, therefore, at an even lower risk for sudden death than the patients in the Mather study. Of the patients allocated to home treatment, 26 eventually required hospital care, mostly for control of pain. Finally, the Nottingham trial suffered from a lack of statistical power. The trial would have needed five times as many patients to detect a reduction in MI mortality from 15% to 10% with a probability of 90%.[2]

At best, studies on the value of coronary care for myocardial infarction have been inconclusive. While nonrandomized studies showed that coronary care reduced short-term mortality, randomized clinical trials did not. Although the Nottingham paper was published nine years ago, the controversy that it engendered continues to this day.[9-17] I am unaware of any study published since then that contributes to the resolution of this problem, and it is highly unlikely that one will be done in the future.

It can be argued that the clinical trials of the 1970s are no longer relevant, that patients have somehow changed, and that new interventions such as bypass operations and coronary angioplasty have made coronary care even more imperative for patients with myocardial ischemia. Some of these claims may, in fact, be true. Nevertheless, it should be remembered that the benefits of coronary care are more presumed than proved. Even if survival from myocardial infarction is improved by these newer interventions, the independent contribution of coronary care should be assessed.

Coronary Care and the Decline in Mortality From Cardiovascular Disease

As we have seen, the mortality rate from cardiovascular disease has fallen steadily since 1968. There are two possible explanations for this trend. One is that the incidence of coronary artery disease has decreased because of changes in cardiac risk factors. Another is that medical interventions, such as coronary care, have improved the survival of patients with myocardial infarction. If the latter were true, then population-based studies of myocardial infarction should show that short- or long-term survival has improved in the past 20 years.

Each of the seven studies in Table 1 examined the mortality of myocardial infarction two or more times during the interval in question.[30-36] While some of these studies showed an improvement in short-term survival,[30,36] others found little[32] or no[34] change. Perhaps the most interesting study is that of Pell and Fayerweather.[31] These authors examined the 24-hour and 30-day case-fatality rates for men employed at the Du Pont Company from 1957 to 1983. The 24-hour case-fatality rate in 1957 to 1959 was 25.1% compared with 21.6% in 1981 to 1983. Because these deaths are usually caused by arrhythmias and occur immediately after the onset of symptoms, it is not surprising that there has been little change. The decline in the 30-day case-fatality rate between 1957 to 1959 and 1981 to 1983 was larger (30.4% versus 24.3%). Most of the decrease did not occur until 1975 to 1977, however, presumably long after the use of coronary care units became a standard of practice.

Perhaps even more disturbing are data on long-term prognosis for patients surviving their first MI. Of the five studies[30,32,33,35,36] in Table 1 providing long-term (2½ to 5 years) follow-up, only one[36] has shown significant improvement in survival over time. Because that study was the most recent one, there is hope that newer interventions have finally made a difference. Thus, population-based studies have not provided consistent support for the hypothesis that a reduction in short-term mortality in myocardial infarction is responsible for the change in cardiovascular mortality. Moreover, it has been difficult to show that secondary prevention and better medical care have improved the long-term prognosis of patients who survive their first myocardial infarction.

Population-based studies do not provide information about the effect of coronary care per se on cardiovascular mortality. It would be very helpful to know the number of lives saved each year because patients with myocardial in-

farctions are admitted to coronary care units. Such estimates were provided by Goldman and Cook in 1984.[2] They used pooled data from several clinical trials to estimate the number of lives saved by resuscitative measures in coronary care units between 1968 and 1976. The analysis was based on the assumption that primary ventricular fibrillation occurs in 4.5% of patients with acute myocardial infarction and that the mortality from that arrhythmia is 87% in the outpatient setting and 12% in the coronary care unit. They also assumed that heart block occurs in 2.3% of patients with MI and that coronary care units reduce its mortality from 52% to 34%.

Goldman and Cook found that 85,000 more people were alive in 1976 because of resuscitative measures in the coronary care unit than would have been in the absence of such measures. Coronary care units, however, accounted for only 13.5% of the total number of lives saved by all cardiovascular interventions. The rest could be explained by the treatment of hypertension and hypercholesterolemia, modification of smoking habits, coronary bypass surgery, better prehospital care, and the medical therapy for ischemic heart disease. The estimated number of lives saved in the coronary care unit each year—19,800—is also disappointing when one considers the number of cardiac beds in operation at this time—more than 13,000 in 1976. Thus, coronary care accounts for one of every seven lives saved by all cardiovascular interventions, a proportion that is disturbing when one considers the resources committed to this form of treatment.

Benefits of Coronary Care for Patients With Chest Pain

Based on the studies that we have reviewed, it is possible to assess the benefit of coronary care for patients who are admitted for the evaluation of chest pain. Patients with documented arrhythmias, hypotension, pulmonary edema, or pericarditis would probably be admitted to a coronary care unit whether an MI is documented or not. Thus, the risk of alternative forms of treatment is confined to those with uncomplicated myocardial infarctions in whom primary ventricular fibrillation or heart block develops. Fineberg and associates[21] calculated that the risk of death from primary ventricular fibrillation was 0.05% for such patients in a coronary care unit and 3.9% for those given outpatient care. They estimated the risk of death from heart block at 0.8% for coronary care unit patients and 1.2% for outpatients. Thus, coronary care saves the lives of 4.3% of those who present with an uncomplicated myocardial infarction compared to a strategy involving only outpatient care.

The benefit of coronary care for patients with chest pain depends on the proportion of patients who have a documented myocardial infarction and the diagnoses for those who do not. Table 2 shows that the proportion with myocardial infarction is remarkably constant for different types of hospitals and for different parts of the country. About 15% of patients who present to an emergency department with chest pain are eventually given the diagnosis of MI. For patients admitted to a coronary care unit, this number is about 30%. It is unclear if patients whose myocardial infarctions are "ruled in" have a different prognosis than those who meet diagnostic criteria in the emergency department. One possibility is that patients who are given a late diagnosis sustain their infarctions immediately after admission. Because they are monitored during the period of highest risk,[1] the benefits of coronary care would be great. On the other hand, patients who are "ruled in" may have smaller infarctions that are more difficult to detect. Because the risk of primary ventricular fibrillation may depend on the amount of ventricular dysfunction,[38] they would be at very low risk. In any event, if we assume that those for whom an MI is "ruled out" are healthy, then coronary care saves the lives of no more than 1% to 2% of those admitted to hospital with chest pain.

Unfortunately, patients whose myocardial infarctions are

TABLE 1.—*Trends in Survival of Patients With Myocardial Infarction (MI)*

Study	*Subjects*		*Comparison, %*		
Rochester, Minnesota	Patients with first MI		1965-1969	*v*	1970-1975
—Elveback et al, 1981[30]	30-day CFR		18.7		9.0
	5-year mortality		40.0		34.0
Du Pont Study	Male employees with first MI		1957-1959	*v*	1981-1983
—Pell and Fayerweather, 1985[31]	30-day CFR		30.4		24.3
Worcester Heart Attack Study	Residents of Worcester, Massachusetts		1975	*v*	1981
—Goldberg et al, 1986[32]	In-hospital CFR		22.1		17.4
	2½-year mortality		(no difference)		
Health Insurance Plan Study	Male patients with first MI		1961-1970	*v*	1971-1978
—Weinblatt et al, 1982[33]	4½-year mortality		(no difference)		
Boston, Massachusetts	Patients of 63 hospitals in Boston		1973-1974	*v*	1978-1979
—Goldman et al, 1982[34]	In-hospital CFR		22.0		23.0
Baltimore, Maryland	Residents of Baltimore		1966-1967	*v*	1971
—Goldberg et al, 1979[35]	In-hospital CFR		27.5		20.0
	5-year mortality		36.0		39.0
Minnesota Heart Survey	Residents of Minneapolis-St. Paul		1970	*v*	1980
—Gomez-Marin et al, 1987[36]	30-day CFR	(men)	19.0		13.0
		(women)	29.0		20.0
	4-year mortality	(men)	28.0		21.0
		(women)	32.0		27.0

CFR=case-fatality rate

TABLE 2.—*Proportion of Patients With Chest Pain Who Have Myocardial Infarction*

Series	Emergency Department, %	Coronary Care Unit, %
Boston City Hospital—Pozen et al, 1980[37]	17*	..
University of Pennsylvania—Eisenberg et al, 1979[3]	16	32
Brigham and Women's Hospital—Lee et al, 1987[4]	16	26
Six-hospital survey—Lee et al, 1987[5]	16	30
Indiana University Hospital—Tierney et al, 1985[6]	11	34
New York Hospital—Fuchs and Scheidt, 1981[7]		30†

*Includes patients with unstable angina.
†Does not include patients with "possible" myocardial infarction.

ruled out are not healthy. Schroeder and colleagues at Stanford University[39] showed that patients with ischemic chest pain who did not have an MI had the same long-term prognosis as those who did. Moreover, patients with crescendo angina may be at high risk for myocardial infarction and sudden death.[40] Finally, there are studies that suggest that signs and symptoms of heart failure or arrhythmias are ominous findings,[7] even in the absence of chest pain.[41] Thus, my comments about the value of coronary care for patients with chest pain do not apply to those with crescendo angina, heart failure, or symptoms and signs of an arrhythmia. An appropriate diagnosis should be vigorously pursued in those in whom an MI is ruled out because the prognosis for some of these patients is poor.

Alternative Strategies

Because conventional ways of ruling out a myocardial infarction are not cost-effective, we should spend a moment reviewing alternative strategies. Although there are a large number of studies in this area, they have used two basic approaches: preadmission screening and early discharge. Most of these studies have also used one of two end points: the early diagnosis of myocardial infarction and the prediction of cardiac complications. I would like to review a few studies that use these approaches and end points.

Perhaps the best example of preadmission screening for patients with chest pain was published by Pozen and associates at Boston University.[37] They developed a multivariate model that used nine clinical variables available in emergency departments to predict the presence of acute ischemic heart disease. When these probabilities were given to the admitting physicians, the proportion of false-positive diagnoses decreased from 51% to 33%. The proportion of false-negative diagnoses, however, was unchanged—3%. A similar instrument using seven clinical variables was later validated in a multicenter clinical trial.[42] When computer-derived probabilities were provided to admitting physicians, the number of coronary care unit patients without acute ischemic heart disease decreased by 30%.

A different approach to preadmission screening was used by Fuchs and Scheidt,[7] who studied interventions required by 414 patients admitted to the coronary care unit of New York Hospital. Almost all interventions occurred in a high-risk group that had one or more of the following findings on admission: ongoing chest pain, pulmonary rales, or one or more premature ventricular contractions recorded on the admission electrocardiogram. Of 306 high-risk patients, 41% received intervention and 4% died. Of 108 low-risk patients, only 6% required intervention and none died. There is also evidence that symptoms of ventricular dysfunction and arrhythmias on admission to a CCU are predictive of complications after the first 24 hours.[41]

Mulley and co-workers[43] examined a strategy involving risk stratification and early transfer for coronary care unit inpatients. They found that 360 patients could be divided into three risk groups on the basis of early complications, serum creatine kinase levels, and the results of an electrocardiogram (ECG) taken within 24 hours of admission. A low-risk subset comprised 168 patients (47%) with no enzyme elevations, ECG abnormalities, or early complications. Criteria for myocardial infarction subsequently developed in only 3%, 2% had late complications, and none died.

Similar findings were reported by Lee and associates.[5] They studied 1,460 patients admitted to a coronary care unit for acute chest pain. Of these, 431 (30%) were eventually given the diagnosis of myocardial infarction. The diagnosis was made within 24 hours of admission in 415 (96%). Of the remaining 16 patients with MI, 9 (56%) had recurrent ischemic pain within the first 24 hours. These results were validated on an independent set of 275 patients; 99% met the diagnostic criteria for myocardial infarction or had recurrent pain within 24 hours of admission.

Summary and Conclusions

The use of medical interventions is often determined by factors other than their effect on a patient's illness. These factors can be emotional, ethical, legal, financial, or academic in nature. The coronary care unit is certainly no exception. For instance, an admission to a CCU might be justified for a patient with chest pain simply because it alleviates the patient's anxiety. Other admissions might be warranted because third-party payers will not support any other decision or because the risk of malpractice is too great to send the patient home. Still others may serve an educational or research purpose. It is unrealistic to assume that these issues are unimportant and that they can be swept aside.

Our discussion concerns one aspect of the use of coronary care units for patients with chest pain—their effect on patient survival. I realize that the other issues have become so large that the actual benefit of coronary care may no longer be relevant. Nevertheless, there are valuable lessons to be learned by reviewing this topic. Although coronary care units have become an integral part of American medicine, several new interventions have not. In the future, we must be sure that patient expectations, legal standards, and financial returns for these interventions are based on a realistic assessment of their clinical benefit and not only on their popularity.

Most of the articles that we have reviewed suggest that coronary care units reduce the mortality from myocardial infarction. This claim has been the subject of controversy, however, and there is little hope that it will be resolved by further study. Compared with modifying risk factors, coronary care has played a relatively small role in the decline in coronary mortality rates in the past 20 years. Nevertheless, the most recent population-based study suggests that secondary prevention and new interventions may improve the long-term outlook for hospital survivors.

Only a small proportion of patients presenting to an emergency department with uncomplicated chest pain are at risk for sudden death from ventricular fibrillation or heart block. The admission of all of these patients to the coronary

care unit is not cost-effective unless preadmission screening or early transfer policies are in effect. Because patients, resources, and social factors vary from institution to institution, it is unreasonable to expect that one strategy is appropriate for all circumstances. Several studies suggest that coronary care unit patients with early complications, signs or symptoms of ventricular dysfunction or arrhythmias, or recurrent ischemic chest pain are at high risk for late complications. Others should be screened for transfer after 24 hours in hospital. Because some patients in whom an MI is ruled out have a poor prognosis, an appropriate diagnosis should be pursued in another setting. Ruling out a myocardial infarction should not be considered an end point for a patient's evaluation.

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Pheochromocytoma—Recent Advances in Diagnosis and Treatment

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs Homer A. Boushey, Professor of Medicine, and David G. Warnock, Associate Professor of Medicine, under the direction of Dr Lloyd H. Smith, Jr, Professor of Medicine and Associate Dean in the School of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, School of Medicine, San Francisco, CA 94143.

RICHARD K. ROOT, MD*: *Presenting this Medical Staff Conference, which deals with recent advances in the diagnosis and treatment of pheochromocytoma, is Neal Benowitz, MD, Professor of Medicine and Chief of the Division of Clinical Pharmacology and Experimental Therapeutics of the University of California, San Francisco (UCSF). Paul Noble will summarize this case.*

PAUL NOBLE, MD†: A 58-year-old black man with hypertension was admitted in January 1987 for an exploratory laparotomy. The patient had been in his usual state of health until December 1986 when he was seen at another hospital for symptoms of pulmonary edema with rapid atrial fibrillation and hypertension. His hospital course was complicated by ventricular tachycardia and ventricular fibrillation. A renal angiogram showed normal renal vasculature, but an abnormal blush was noted at the aortic bifurcation. His 24-hour urinary catecholamine excretion was increased. He was transferred to UCSF, where a repeat urine vanillylmandelic acid (VMA) level was within normal limits, with a mildly elevated metanephrine concentration. A thallium scan taken during an exercise tolerance test disclosed a nonreversible inferoapical defect. Echocardiographic study showed moderate left ventricular hypertrophy, impaired diastolic compliance, mild left ventricular dilatation, mild aortic insufficiency, aortic sclerosis, and septal hypokinesis, with an overall ejection fraction of 40% to 50%. Electrophysiologic studies showed no sustained ventricular tachyarrhythmias. Serum catecholamine levels were borderline. An abdominal magnetic resonance imaging (MRI) scan disclosed a 2 by 3 by 3-cm mass at the level of the aortic bifurcation. Radioisotope scanning showed no uptake.

The patient remained hemodynamically stable throughout his hospital stay. On readmission in January, he was feeling well and had no symptoms. He said he had had no complications or diaphoresis currently or in the past. There was a history of headaches since the 1960s. His medical history revealed hypertension and mild renal insufficiency. His medication regimen included propranolol hydrochloride, 20 mg four times a day; clonidine hydrochloride, 0.1 mg four times a day; prazosin hydrochloride, 4 mg three times a day; furosemide, 40 mg twice a day; and potassium. He had a smoking history of 60 pack-years.

On physical examination his blood pressure was in the range of 180 to 190/80 to 110 mm of mercury, pulse rate 80 beats per minute, respirations 15, and temperature 36.5°C (97.7°F). He was thin and well developed. There were grade I hypertensive retinal changes. His lungs were normal, and there was no elevated jugular venous pressure. Heart sounds were normal, with a II/VI crescendo-decrescendo systolic murmur that radiated across the precordium into the neck. A II/VI early diastolic murmur was also present at the left lower sternal border. The point of maximum impulse was laterally displaced. No bruits were heard, and pulses were intact. The abdomen was normal; superficial varicose veins were present in his legs. His neurologic examination showed no abnormalities.

Laboratory studies at that time revealed normal serum levels of electrolytes and calcium, a blood urea nitrogen level of 22 mg per dl, creatinine 1.5 mg per dl, albumin 3.3 grams per dl, and normal complete blood count and urinalysis. Chest radiographs showed no evidence of acute disease. An electrocardiogram (ECG) showed sinus bradycardia at a rate of 58, left anterior fascicular block, and left ventricular hypertrophy by voltage associated with inferolateral ST-T wave abnormalities.

Hospital course. The patient's hypertension was controlled by adding phenoxybenzamine hydrochloride, 5 mg twice a day, which was gradually increased to 60 mg a day. The systolic blood pressure remained elevated in the range of 140 to 180 mm of mercury, and orthostatic changes of more than 15 mm of mercury were noted. His intravascular volume was repleted, and he underwent a laparotomy with removal of a 4 by 6 by 4-cm mass overlying the vena cava at the level of the aortic bifurcation. No other lesions were discovered. Perioperative hemodynamic findings included moderate elevations of the blood pressure. There were no cardiovascular or other complications. A frozen section study indicated the presence of a pheochromocytoma. A stained specimen suggested the presence of a nonmalignant tumor of neuroectodermal origin. After discharge, the patient has been easily maintained on a regimen of clonidine, metoprolol tartrate, and prazosin without further problems.

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ABBREVIATIONS USED IN TEXT

COMT = catecholamine-*o*-methyltransferase
CT = computed tomographic
MAO = monoamine oxidase
MIBG = metaiodobenzylguanidine
MRI = magnetic resonance imaging
UCSF = University of California, San Francisco
VMA = vanillylmandelic acid

NEAL L. BENOWITZ, MD*: This case presents an opportunity to discuss new concepts of the pathophysiology, diagnosis, and treatment of pheochromocytoma. Pheochromocytoma is not a common tumor; it has been described as occurring in 1 of every 1,000 patients with hypertension. This means that it will occur among the patients served by most hospitals but not among those cared for by most individual practitioners. Many cases of pheochromocytoma are probably not diagnosed. When diagnosed, the disease is often in an advanced stage. This is because the clinical presentation is highly variable, and the results of diagnostic studies in some cases are not definitive.

To summarize the salient points about this patient, he is a 58-year-old man who had hypertension, as far as we know, for three years. We do not know if his hypertension was labile. When seen he had pulmonary edema with cardiac arrhythmias. The findings of a renal angiogram, presumably done to rule out possible renovascular hypertension, suggested the diagnosis. The level of urinary catecholamine metabolite excretion was borderline. Plasma catecholamine concentrations were elevated at the time he was acutely ill but returned to normal some time later on. A thallium study suggested an old myocardial infarction. An ECG showed left ventricular hypertrophy, as did an echocardiogram, which also showed left ventricular dilatation and a reduced ejection fraction. His serum catecholamine values were slightly elevated; an MRI scan was abnormal, and the metaiodobenzylguanidine (MIBG) scan was normal. His blood pressure was fairly well controlled with the administration of prazosin and β-blockers before surgical treatment. He had persistent hypertension following the laparotomy.

Adrenal pheochromocytoma is a solid, highly vascular tumor that typically contains areas of hemorrhage and focal necrosis. Spontaneous hemorrhage or necrosis may explain the paroxysms of hypertension that occur in some patients. Normal adrenal glands contain pleomorphic cells without abundant granular cytoplasm. The cells are found in cords or clusters. It is difficult to differentiate between benign and malignant pheochromocytoma by histologic examination, so the comment that a diagnosis of a benign tumor was made from a histologic section must be questioned. On electron microscopy, material corresponding to a large number of secretory granules is seen within the adrenal or pheochromocytoma cell. Catecholamines are bound within these granules and are released by exocytosis (Figure 1). One physiologic stimulus to exocytosis is acetylcholine, which is released by activation of the splanchnic sympathetic nerves. Calcium influx is thought to be a trigger for exocytosis.

Normal adrenal glands contain mostly epinephrine. In pheochromocytoma cells, there may be high concentrations of norepinephrine, epinephrine, and, in some cases, dopamine. Most pheochromocytomas secrete predominantly nor-

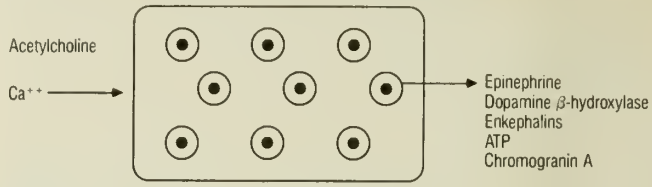

Figure 1.—Catecholamines and other chemicals are released by exocytosis from chromaffin granules of the adrenal medullary cell. ATP = adenosine triphosphate

epinephrine; about 15% of them secrete predominantly epinephrine. Dopamine β-hydroxylase, an enzyme that converts dopamine to norepinephrine, and endogenous opiates, whose physiologic role within the adrenal glands is not entirely clear, are also found within the granules. The release of endogenous opiates from the adrenal glands may play a role in stress-related analgesia. Naloxone hydrochloride given in large doses causes catecholamine release and can precipitate a hypertensive crisis in patients with pheochromocytoma.[1] Adenosine triphosphate in granules is thought to provide some of the energy involved in the binding and sequestration of catecholamines. Chromogranin A, a soluble protein, is one of the major binding proteins in the granule. Chromogranin A can be measured by radioimmunoassay and has been used as a diagnostic test for pheochromocytoma, although it is also found in the blood of patients with other neuroendocrine-secreting tumors.[2]

Why is the pattern of catecholamine release and related clinical manifestations among persons with pheochromocytoma so variable? Tyrosine is present in large quantities in catecholamine-secreting cells. Tyrosine hydroxylase is the major enzyme that limits the formation of catecholamines. The amount of tyrosine hydroxylase in a tumor is an important indicator of how much catecholamine is synthesized. Metyrosine (α-methyl-L-tyrosine), a drug that blocks tyrosine hydroxylase, may be used therapeutically to reduce catecholamine synthesis by the tumor. The use of this drug will be discussed in more detail later. Dopamine β-hydroxylase, responsible for converting dopamine to norepinephrine, may be missing in immature tumors. Thus, the presence of a tumor secreting predominantly dopamine indicates a higher probability of malignancy.[3] In the patient presented at this conference, the plasma epinephrine level was normal, while norepinephrine and dopamine values were elevated, suggesting the possibility of a malignant tumor.

Newer Concepts in Pathophysiology

Circulating catecholamine levels do not correlate strongly with blood pressure in pheochromocytoma.[4] If catecholamines are responsible for hypertension, why are blood pressure and catecholamine levels not correlated? Four factors are probably important. The first is blood volume. Blood volume tends to be low in patients with pheochromocytoma because of persistent vasoconstriction.[5] Hypovolemia probably explains at least in part the increased prevalence of orthostatic hypotension in patients with this tumor. The findings of severe hypertension and orthostatic hypotension should suggest the diagnosis of pheochromocytoma. Hypovolemia may also contribute to life-threatening shock, which may follow surgical removal of the tumor.

The second factor is secretion of vasodilators by the tumor. Dopa, prostaglandins, and other vasodilating substances may be secreted by pheochromocytomas. The 10%

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to 15% of patients with pheochromocytoma who do not have hypertension are the ones likely to have tumors secreting dopa and dopamine.[6] Some patients with epinephrine-secreting tumors have intermittent hypertension. Thus, in many tumor cases, the blood pressure is determined by a balance of the release of vasoconstrictor and vasodilator substances.

A third factor is receptor down-regulation. As a consequence of high levels of catecholamines bathing vascular smooth muscle cells, the sensitivity of these cells is decreased. This may occur by a decrease in the number of receptors or an alteration in receptor-effector coupling.[7] Thus, the blood vessels of patients with pheochromocytoma may require extremely high concentrations of catecholamines to constrict and produce hypertension. Because of the receptor down-regulation, therefore, sustained high levels of catecholamines may not cause hypertension.

A fourth factor is the important role played by sympathetic neural control in regulating blood pressure. This may explain why many patients with pheochromocytoma have sustained rather than paroxysmal hypertension. In a Mayo Clinic series of 106 cases, 85% of patients had hypertension, whereas the remainder did not.[8] Of hypertensive patients, about 40% had sustained hypertension without paroxysms. If hypertension is due to the release of catecholamines from the tumor, why do many patients have sustained hypertension? A possible answer to this question has come from studying the effects of the use of clonidine in patients with pheochromocytoma.[9] Clonidine acts on the brain to decrease sympathetic neural discharge. In patients with essential hypertension, clonidine decreases the blood pressure by reducing sympathetic outflow, which is associated with a fall in circulating catecholamine levels. In pheochromocytoma patients, clonidine decreases the blood pressure to the same degree as in patients without pheochromocytoma, but there is no change in their plasma catecholamine levels. This suggests that the sympathetic nervous system continues to control minute-to-minute regulation of the blood pressure. Presumably, the high local concentrations of catecholamines at sites of synaptic release have a greater influence on vasoconstriction than do the circulating catecholamines. This also explains how patients with pheochromocytoma maintain unchanged their blood pressure with postural shifts and other circulatory stresses. Sustained hypertension in pheochromocytoma patients may be due to the accumulation of increased stores of catecholamines in sympathetic neurons as a consequence of increased circulating levels. Normal physiologic stimuli will then cause the release of greater-than-normal amounts of catecholamines, resulting in sustained hypertension.

Cardiovascular Complications

The patient under discussion had an acute life-threatening cardiovascular illness. In a recent clinical series, ten patients with pheochromocytoma died during a fulminant cardiovascular illness.[10] Pheochromocytoma was diagnosed before death in only two of these patients. Six of the patients had symptoms of chest pain or shortness of breath and four had pulmonary edema. Most died a few days after hospital admission. Five were diagnosed as having a myocardial infarction, although, as will be discussed later, this diagnosis is difficult to make in patients with pheochromocytoma. Two patients died of heart failure, two of stroke, and one of postoperative circulatory collapse after a laminectomy.

What are the major cardiovascular complications of pheochromocytoma? The most common is probably myocarditis, a focal myocardial necrosis, often associated with a varying degree of fibrosis. Administering high doses of catecholamines produces similar pathologic lesions in animals. In a large autopsy series, 15 of 26 patients had evidence of myocarditis with active necrosis, while two had fibrosis without necrosis.[11] Of the patients with myocarditis, 11 died of left ventricular failure. The other four died of stroke, postoperative hemorrhage, and cardiac arrest. Myocarditis should be considered in all patients with pheochromocytoma and is probably the cause in those cases that suggest ischemia as well as heart failure.

A diagnosis of myocardial infarction is ordinarily made on the basis of ECG changes and the presence of cardiac enzymes. In patients with pheochromocytoma in whom myocardial infarction has been diagnosed, however, there is often minimal or no evidence of coronary heart disease. The underlying pathologic disorder may in fact be myocarditis or coronary spasm, both of which can produce ECG changes resembling myocardial infarction and can be associated with cardiac enzyme release, but they can fully resolve with treatment.

Our patient had cardiac arrhythmias, including atrial and ventricular fibrillation. Such arrhythmias are known to be associated with paroxysms and the release of catecholamines in patients with pheochromocytoma. They occur commonly in surgery during resection of the tumor. Arrhythmias are thought to be a major cause of sudden death, which is not uncommon in patients with pheochromocytoma.

Dilated congestive cardiomyopathy, believed to be related to myocarditis, has been well described in patients with pheochromocytoma.[12] Full recovery from severe cardiomyopathy may occur. In a recent case report, a patient had a preoperative ejection fraction of 23%, which increased to 66% six weeks after the tumor was removed.[13] In some cases, however, cardiomyopathy is not reversible, presumably because of extensive scarring and fibrosis.

Hypertrophic cardiomyopathy, which resolves after treatment, has also been described in patients with pheochromocytoma.[14] In a recent series of 26 patients with pheochromocytoma, however, 80% had normal echocardiograms, 20% had left ventricular hypertrophy without hypertrophic changes, and none had asymmetric hypertrophy.[15] Thus, if hypertrophic cardiomyopathy is in fact associated with pheochromocytoma, it must be rare. Another interesting finding in the series was that five patients had ECG evidence of left ventricular hypertrophy but normal echocardiograms.

Undiagnosed Pheochromocytoma

In a series from the Mayo Clinic that spanned 50 years, 75% of the cases were undiagnosed during life.[16] Many were missed even in the 1970s, when most of the current diagnostic methods were available. Only 54% of the patients in whom pheochromocytoma was diagnosed at autopsy were known to have had hypertension, which supports the statement that a large number of patients with the tumor may have normal blood pressures. A quarter of the deaths occurred in relation to surgical procedures, caused by either hypertension or shock following the operation. An unusual cardiovascular response to an operation is an important clue to the presence of pheochromocytoma. A quarter of the patients

had a diagnosis of myocardial infarction, and about 20% a diagnosis of stroke.

Diagnosis

The three elements of diagnosis are clinical suspicion, biochemical tests, and localization studies. Table 1 summarizes the clinical hints of pheochromocytoma. Labile hypertension and paroxysms of hypertension and tachycardia are well-known manifestations of pheochromocytoma. It should be noted, however, that most pheochromocytoma patients do not have tachycardia; most have bradycardia due to reflex cardiac slowing in response to norepinephrine-mediated vasoconstriction. Sustained tachycardia suggests the presence of an epinephrine-secreting tumor. Spells of headache, palpitations, or sweating (or all three) are present in more than 90% of patients.[17] Pallor is very common, and sometimes there is a history that the patient episodically turns white. Flushing is rare in patients with pheochromocytoma, and its presence should suggest another diagnosis. Accelerated hypertension, especially with papilledema, is uncommon and should suggest secondary hypertension, including pheochromocytoma. Unexplained hypermetabolism and weight loss should also suggest pheochromocytoma. A patient at the San Francisco General Hospital and Medical Center had fever of unknown origin and weight loss and had normal blood pressure throughout the hospital course.[18] In a workup for possible gallbladder disease, an abdominal arteriogram revealed an adrenal mass that was later shown to be a dopamine-secreting pheochromocytoma. Both dopamine- and epinephrine-secreting tumors may be associated with a hypermetabolic state with normal blood pressures. Abnormal carbohydrate metabolism, particularly the sudden, unexpected development of diabetes mellitus, should suggest a pheochromocytoma. Unusual hypertensive responses to anesthesia, to any antihypertensive drugs (particularly β-blockers), or to sympathomimetic drugs are useful clues to the presence of the tumor.

The appropriate use of biochemical tests is based on an understanding of catecholamine metabolism (Figure 2). Two major enzymes are involved. Catechol-*o*-methyltransferase (COMT) is found primarily in blood vessels and sometimes in the tumor. Monoamine oxidase (MAO) is found within neurons and in the liver. In a healthy person, 90% of what is excreted in the urine as catecholamines and metabolites is vanillylmandelic acid. This is because most of the metabolism occurs initially within neurons, mediated by MAO and subsequently by COMT in the circulation. The result of these two metabolic steps is the production of VMA. Intravenously infused catecholamines, however, are metabolized primarily by COMT in blood vessels, so that there is greater urinary excretion of normetanephrine and metanephrine as well as unchanged catecholamines. A patient with a pheochromocytoma resembles the infusion model, so there is a greater proportionate increase in metanephrine and free catecholamine concentrations than in VMA levels. Some bulky tumors do contain large amounts of MAO, and in such patients high levels of metanephrines and VMA with normal levels of free catecholamines may be found because the catecholamines are extensively metabolized within the tumor.

The three most useful urine tests are those determining VMA, metanephrines, and catecholamine values. The most important blood tests are those of plasma catecholamine concentrations, which are considered by many authorities to be the most sensitive and specific tests for pheochromocytoma. Studies comparing these concentrations in patients with diagnosed pheochromocytoma to those in patients without the tumor provide some insight into the relative sensitivity of the tests. In such patients, false-negative values were found for urinary VMA in 30%, metanephrines in 10%, and catecholamines in 10%, and in only about 5% for plasma catecholamines.[4,19] Assays of urinary catecholamines and metanephrines are thus adequate to diagnose pheochromocytoma in most patients, but when the results of these studies are equivocal and pheochromocytoma is suggested clinically, plasma catecholamines should be measured.

There may be considerable swings in the levels of plasma catecholamines from time to time, a consequence of postural changes, exercise, emotional arousal, and other factors. Despite such variability, basal concentrations are usually increased severalfold in patients with pheochromocytoma. Plasma catecholamine measurement is generally standardized by drawing blood specimens with a catheter that has been in place for 20 or 30 minutes, with the patient at rest. The diagnosis of dopamine-secreting tumors is more difficult with the use of plasma measurements. Most assays measure free (unconjugated) dopamine, whereas in the plasma, 99% of dopamine is conjugated.[20] Thus, conjugated dopamine levels in the plasma may be extremely high, but free dopamine levels may be only minimally elevated. To diagnose a dopamine-secreting pheochromocytoma, assays of urinary dopamine may be much more sensitive.

Based on testing of plasma catecholamine levels in medically stable patients at rest, a diagnostic cutoff has been set for pheochromocytoma at about 1,000 pg per ml.[19] False-negative tests will occur, but the biggest problem in clinical practice is nonspecificity due to false-positive tests in acutely

TABLE 1.—*Clinical Hints of Pheochromocytoma*

Unusual lability of blood pressure
Paroxysms of hypertension and tachycardia
Spells of headache, palpitations, pallor, perspiration
Accelerated hypertension
Hypermetabolism and weight loss
Abnormal carbohydrate metabolism
Pressor response to induction of anesthesia or to antihypertensive or sympathomimetic drugs
Suprarenal or midline abdominal mass

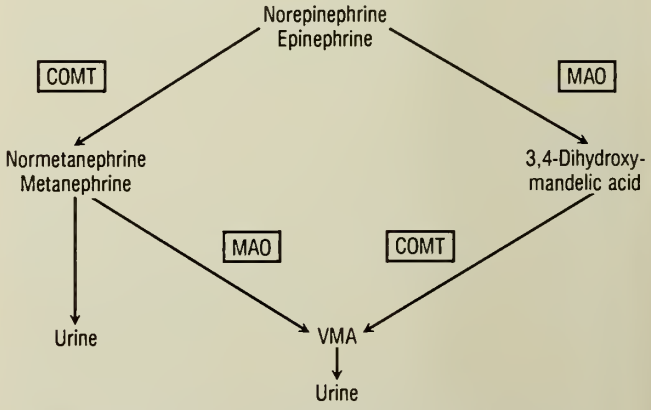

Figure 2.—The diagram shows the pathways of catecholamine metabolism. COMT = catechol-o-methyltransferase, MAO = monoamine oxidase, VMA = vanillylmandelic acid (3-methoxy-4-hydroxymandelic acid)

ill patients. These patients have increased catecholamine secretion as part of their diseases. Where possible, plasma catecholamine studies should be done when patients are medically stable and taking no medications. In some cases it is necessary to admit a patient to hospital to stop medication intake under supervision to do a proper diagnostic evaluation.

A conservative approach to interpreting plasma catecholamine values is as follows: concentrations of more than 2,000 pg per ml are considered abnormal, those of less than 500 pg per ml are normal, and those of 500 to 2,000 pg per ml are equivocal, should be repeated, and may require confirmation by pharmacologic testing.

It is fortunate that biochemical studies are usually diagnostic, for pharmacologic tests are potentially hazardous. For example, phentolamine testing may result in shock, and histamine or tyramine stimulation tests may produce life-threatening hypertension. We occasionally do clonidine suppression tests, however, primarily in patients with hypertension who have borderline catecholamine values. The test consists of measuring plasma catecholamine concentrations at rest before and three hours after administering 0.3 mg of clonidine.[21] In patients with essential hypertension, clonidine induces a fall in plasma catecholamine levels to less than 500 pg per ml. In patients with pheochromocytoma, plasma catecholamine levels remain unchanged because tumor secretion is not suppressed by clonidine. The clonidine suppression test is not 100% sensitive but is fairly useful in evaluating equivocal cases. In patients with epinephrine-secreting tumors, clonidine may suppress norepinephrine but not epinephrine.

Glucagon provocation tests are used occasionally in patients with suspected pheochromocytoma but normal blood pressures. Glucagon acts directly on the tumor to induce release of catecholamines but does not cause release from a normal adrenal gland. A rapid infusion of 2 mg of glucagon produces a greater than twofold increase in plasma catecholamines and a hypertensive response in most patients with pheochromocytoma. Phentolamine should be available to treat a hypertensive crisis.

Localization

After a diagnosis of pheochromocytoma has been made biochemically, the tumor must be located to plan surgical excision.

About 90% of pheochromocytomas are located in an adrenal gland, with a 2:1 preference for the right over the left side. The other 10% are found in other areas where there is chromaffin tissue, including along the para-aortic sympathetic chain, within the organ of Zuckerkandl (at the aortic bifurcation), and in the wall of the urinary bladder. Less than 1% are extra-abdominal, involving the sympathetic chain in the neck or mediastinum.

The most useful and safest radiologic test for localization is the computed tomographic (CT) scan of the abdomen, which detects more than 95% of adrenal masses.[22] Where there is a clinical suggestion of pheochromocytoma and the adrenal CT scan is normal, a scan after the administration of MIBG labeled with iodine 131 is indicated. MIBG is a radiopharmaceutical that concentrates in catecholamine-secreting tumors and is detected by scintigraphic techniques.[23] In contrast to other radiologic studies, the MIBG scan is a physiologic test. It allows localization on the basis of pharmacologic activity and is particularly useful in detecting extra-adrenal pheochromocytomas and in confirming that an adrenal mass is indeed a functional pheochromocytoma rather than a benign adenoma. The use of an MIBG scan may be considered even when an abdominal CT scan is abnormal because of the possibility of bilateral adrenal pheochromocytoma or metastatic pheochromocytoma—findings that may influence management. The sensitivity of the MIBG scan is 80% to 90%, and specificity is 100%.

TABLE 2.—*Medical Management of Pheochromocytoma*

Treatment Goal	*Drug Therapy*
Treatment/prevention of hypertensive crisis	Phentolamine mesylate Sodium nitroprusside
Preoperative control of blood pressure	Phenoxybenzamine hydrochloride Prazosin hydrochloride Labetalol hydrochloride Captopril, enalapril maleate Nifedipine, verapamil Metyrosine (Demser)
Management/prevention of arrhythmias	β-Blockers (only after α-blockade)

Magnetic resonance imaging is an alternative to CT scanning for detecting and localizing pheochromocytomas. It may have some advantages, including better differentiation of small adrenal masses from surrounding tissues, a greater capacity to distinguish between many different types of adrenal lesions, and there is no need for the intravenous administration of contrast material or for irradiation.[24,25]

Other localization tests such as adrenal angiography and selective venous catheterization and obtaining plasma specimens from the adrenal or other sites for measuring catecholamines are potentially hazardous and are now rarely used.

Medical Therapy

Rational therapy for pheochromocytoma requires a clear idea of what is being treated. There are two treatment goals. The first is to treat or prevent further cardiovascular complications, including hypertensive crisis, myocardial injury with heart failure, and arrhythmic sudden death. The second goal is to prepare the patient for surgical intervention.

The mainstay of therapy is the administration of α-adrenergic blocking drugs to reverse the effect of excessive concentrations of catecholamines. Drugs used in the medical management of pheochromocytoma are listed in Table 2. Hypertensive crisis, either preoperatively or in the operating room, may be managed with the parenteral administration of phentolamine hydrochloride, an α-blocker, or sodium nitroprusside.

Control of the blood pressure preoperatively is considered by most authorities to be important in preparing for surgical treatment to allow stabilization of cardiovascular complications, to provide some baseline antihypertensive drug effect before an operation, to permit vascular volume repletion, and to allow resensitization of adrenergic receptors.[26] Volume repletion and resensitization of receptors may reduce the severity of postoperative hypotension, which may be life-threatening. The most frequently used preoperative treatment has been the administration of phenoxybenzamine hydrochloride, a long-acting, noncompetitive α-adrenergic blocker. Because of the noncompetitive nature of the blockade, it is more difficult for catecholamines released by the tumor to overcome the blocking effects of phenoxybenza-

mine. The major complication of phenoxybenzamine is orthostatic hypotension, which may be severe. Doses are generally as high as 80 to 100 mg per day, as tolerated by the severity of orthostatic hypotension. Prazosin hydrochloride is a shorter-acting α-blocking drug that has been used with some success preoperatively but seems to provide less intraoperative blood pressure control.[27] Labetalol hydrochloride is a combined α- and β-adrenergic blocker that can be administered intravenously or orally and may be potentially useful in the presence of tachycardia—that is, where there is considerable epinephrine secretion.[28] Angiotensin-converting enzyme inhibitors may reduce the blood pressure, presumably because of the known effect of catecholamines to increase renin release, which results in activation of the renin-angiotensin-aldosterone system.[29] Calcium antagonists, including nifedipine and verapamil, may be useful in managing pheochromocytoma patients who have cardiovascular complications, for several reasons. Calcium is a trigger for catecholamine release from the tumor. Case reports describe reduced urinary catecholamine secretion in patients with pheochromocytoma after calcium blocker therapy.[30,31] Excessive calcium entry into the cells is believed to contribute to the pathogenesis of catecholamine-mediated myocarditis. Finally, calcium antagonists might prevent catecholamine-mediated coronary spasm.

Metyrosine (Demser) is a "false" catecholamine precursor that inhibits the enzyme tyrosine hydroxylase, the rate-limiting enzyme in catecholamine synthesis. Metyrosine reduces catecholamine synthesis by 40% to 80%.[32] It is used primarily in patients with malignant or inoperable pheochromocytoma, but can also be used preoperatively in low doses in patients whose blood pressure is difficult to control with other medications. The side effects of metyrosine are troublesome and include excessive sedation, depression, tremor, muscle stiffness, and crystaluria.

Cardiac arrhythmias are primarily mediated by β-adrenergic effects and are most appropriately treated with β-blockers. When, however, propranolol or another nonselective β-blocker is given to patients with pheochromocytoma without prior α-adrenergic blockade, aggravation of hypertension, pulmonary edema, or both may ensue.[33] Nonselective β-blockers antagonize the catecholamine β-mediated vasodilation while leaving the α-mediated vasoconstriction intact, resulting in increased vascular resistance, aggravated hypertension, and a sharply increased cardiac afterload. In addition, cardiac contractility may be dependent on β-adrenergic stimulation in pheochromocytoma patients. Thus, although β-blockers are the drugs of choice for catecholamine-induced arrhythmias, they should be given only after effective α-blockade and should be administered cautiously, beginning with a low dose and titrating the dose gradually as tolerated.

Considering all the available drugs, it seems most logical to use phenoxybenzamine as the primary agent to control blood pressure, adjusting the dose on the basis of tolerable orthostatic hypotension, and adding other agents to improve blood pressure control and to treat other complications. It is common practice to attempt to control the blood pressure for two to four weeks before surgical excision.

A discussion of surgical treatment and anesthetic management of pheochromocytoma is beyond the scope of this review. Internists should recognize that tumor manipulation is often associated with severe hypertension and arrhythmias, and that removal of the tumor is often followed by severe hypotension, requiring the administration of fluids and pressors. Before the 1950s, the surgical mortality for pheochromocytoma was 30% to 45%, mostly due to postoperative shock. Such occurrences should be anticipated in the preoperative medical evaluation of patients.

After the operation, patients should be observed for the persistence or recurrence of hypertension. Hypertension may persist for several days after surgical removal of the tumor due to high levels of catecholamines and the gradual depletion of those stores from neurons. Continued persistence or recurrence of hypertension should raise concern about the possible presence of residual or metastatic pheochromocytoma. In the case presented, persistence of hypertension and the finding of elevated plasma dopamine concentrations raised concern about malignant pheochromocytoma.

In summary, studies of the pathophysiology of pheochromocytoma have been extremely useful in furthering our understanding of the normal functioning of the sympathetic nervous system and of the varying manifestations of pheochromocytoma. Although pheochromocytoma is uncommon, it occurs often enough that practicing internists need to remain vigilant as to its possibility, even in nonhypertensive patients. Pheochromocytoma may present as a catastrophic cardiovascular illness and as such provides a continued challenge in diagnosis and management. This tumor has fascinated physicians for many years and will surely continue to do so.

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Poliovirus Vaccine

I AM FREQUENTLY ASKED ABOUT POLIOVIRUS VACCINE for adults—which one to use. This would be given primarily to travelers or to people who are in high-risk occupations. The health care worker is always listed as being in a high-risk occupation and yet, in fact, I know of no instance where polio has occurred in a health care worker in this country, even in the days when there was no vaccine and a lot of polio.

At any rate, we do recommend poliovirus vaccine for adults. And if your patient is unimmunized or is uncertain, which is the usual scenario, then we do recommend the parenteral vaccine IPV, or Sabin vaccine, if you like. That is given, ideally, at 0, 1 to 2 months, 3 to 4 months, and 12 months. Now, what happens to me is that I have a patient come in and say "I'm going to Thailand, Malaysia, Tibet, and another country I have not heard of, and I'm leaving in three days. What should I do?" Unfortunately, that 12-month scenario, for someone who has never been immunized, is not possible, and then you're left with a very unpleasant choice. If this person has been previously immunized, has had at least three doses of any polio vaccine, even if they're not sure which one, then you can go right ahead with a booster dose of oral polio vaccine. That's only required about every ten years—and the "every ten years," I can assure you, is a number that is based on no science at all. I was on the committee that decided that that sounded right. We didn't have any data and we still don't have any data, but that's the current recommendation.

If, however, your traveler has not been immunized, or isn't at all sure whether they've ever been immunized, and is leaving fairly soon, so you don't think you can get at least two IPVs in, that is, leaving within two months of when they come to see you, which is my usual experience, then you might wish to consider oral polio vaccine simply because for a single dose, a larger proportion of travelers will be immunized.

—ELIZABETH BARRETT-CONNOR, MD

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Epitomes
Important Advances in Clinical Medicine

Chest Diseases

The Scientific Board of the California Medical Association presents the following inventory of items of progress in chest diseases. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, research workers, or scholars to stay abreast of these items of progress in chest diseases that have recently achieved a substantial degree of authoritative acceptance, whether in their own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Chest Diseases of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to Division of Scientific and Educational Activities,
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Benefits of Hyperbaric Oxygen Therapy in Infectious Disease

HYPERBARIC OXYGEN greatly enhances the effectiveness of conventional therapy in treating necrotizing soft tissue infections, refractory osteomyelitis, and infected ischemic wounds. The mechanisms of this therapy explain its beneficial effects. Tissue oxygen tension has been found to be substantially reduced in infected tissue. Standard hyperbaric oxygen treatment increases the oxygen tension to normal or above normal in infected tissues. Tissue oxygen tensions increase with repetitive treatments. The increased oxygen tension produced by hyperbaric oxygen leads to the enhanced production of superoxide, hydrogen peroxide, and other toxic oxygen radicals.

Thereby, on strict anaerobic organisms, hyperbaric oxygen has a direct bactericidal effect through the production of toxic radicals. Anaerobic organisms are extremely sensitive to these oxygen radicals because most lack the superoxide-degrading enzyme, superoxide dismutase, and the hydrogen peroxide-degrading enzyme, catalase. In contrast to anaerobic organisms, hyperbaric oxygen has no direct effect on aerobic organisms. Hyperoxic conditions induce aerobic organisms to produce increased concentrations of superoxide dismutase. Phagocytic killing of many aerobic organisms is diminished under the hypoxic conditions found in infected tissues. The oxygen-dependent intracellular killing mechanisms of polymorphonuclear leukocytes require oxygen to rapidly kill many aerobic organisms. When the required oxygen is available in infected tissue through the use of hyperbaric oxygen, the level of polymorphonuclear leukocyte killing of aerobic organisms returns to normal or above normal. In addition, the aminoglycoside class of antibiotics does not kill well under low oxygen conditions. Hyperbaric oxygen potentiates the bactericidal effects of tobramycin and possibly other aminoglycosides.

Increased oxygen tension enhances wound healing by facilitating new collagen formation and subsequent angiogenesis. When the environment of fibroblasts has a low oxygen tension—less than 10 mm of mercury—the cells cannot sensitize collagen or migrate appropriately. Hyperbaric oxygen increases the oxygen availability to the fibroblasts and thereby facilitates new collagen formation and subsequent angiogenesis or migration of the ingrowing blood vessels. Hyperbaric oxygen, therefore, promotes faster healing in hypoxic infected wounds not only by increasing the effectiveness of the antibiotics but also by enhancing the collagen production and blood vessel migration.

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Airway Obstruction in Sarcoidosis

THE LUNGS are the most commonly involved organs in patients with sarcoidosis. The granulomata typically occur along lobular septa and are scattered throughout the pulmonary interstitium and alveolar walls. Bronchial or peribronchial granulomata occur frequently, and a granulomatous mass may protrude into the bronchial lumen on occasion. In the past, extensive physiologic studies, with a few exceptions, emphasized functional changes characteristic of restrictive pulmonary disease—that is, reduced static lung volumes, impaired diffusing capacity (transfer factor), and reduced pulmonary compliance. Recently, however, several studies have reassessed airway function in sarcoidosis.

In one study from Greece, airflow obstruction was noted in at least 30% of stage I patients and at least 44% of stage II patients. In another study of 123 consecutive black patients with sarcoidosis, 78 (63%) had reduced ratios of the forced expiratory volume in one second (FEV_1) to the forced vital capacity. Thus, airway obstruction is a common feature of sarcoidosis; the exact incidence of the abnormality varies, depending on racial and genetic factors.

Sarcoid granulomata protrude in the lumen of the airways and influence their function; enlarged lymph nodes may compress bronchi and produce narrowing; finally, in ad-

vanced cases, fibrosis may result in substantial distortion of the breathing tubes. Main, lobar, segmental, and subsegmental airways may all be involved. Decreased lung volumes might account for the flow reduction in many cases. In a large number of cases, however, the pathophysiologic basis of the obstruction seems to be related to bronchial hyperreactivity. Increased bronchial hyperresponsiveness was found in 50% of patients in two studies. We tested 26 patients with sarcoidosis; 18 (60%) showed a 20% or greater fall in FEV_1. It is clear that bronchial hyperreactivity occurs in patients with sarcoidosis, but we do not know why. The recent observation of increased levels of C3, C4, C5, and the anaphylatoxins C3a and C4a in alveolar macrophage supernates from patients with active sarcoidosis opens the door for further studies of the relative role of alveolar macrophage-produced mediators in bronchial hyperreactivity and airway obstruction in sarcoidosis.

Severe airflow obstruction rarely occurs in patients with sarcoidosis. In a few reported cases, bullous emphysema and hyperinflation were most likely related to destruction of the alveolar septa and honeycombing rather than pure airway obstruction. In one study in America, progressive airway obstruction was absent in most of the patients. It should be noted, however, that patient selection might be responsible for relatively better prognoses in European series than in American series.

Treatment with corticosteroids usually produces an improvement in vital capacity and FEV_1 but has a minimal effect on the low compliance and diffusing capacity. Corticosteroid therapy seems to benefit patients with bronchial sarcoidosis. Improvement is most likely achieved by suppressing the active macrophage and switching off the production of complement products and anaphylatoxins responsible for increased airway hyperreactivity and airway obstruction.

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α_1-Protease Inhibitor Deficiency and Pulmonary Emphysema

THE PROTEASE-ANTIPROTEASE THEORY holds that emphysema results from digestion of elastin in areas of the lung subjected to a local excess of elastolytic protease or a deficiency of its inhibitor. This theory originated with two observations reported in the 1960s. One group reported the association between emphysema and a severe, genetically determined deficiency of α_1-protease inhibitor (α_1Pi). Another investigator described an animal model of emphysema resulting from the introduction of proteases into airways. Research over the past two decades supports the hypothesis. Proteases are found on elastic fibers in areas of emphysema. Cigarette smoke oxidatively inactivates α_1Pi, mobilizes excess leukocytes and their elastases to the lungs, causes syntheses of more readily degradable elastic fibers, and directly oxidizes and injures elastin.

Severe α_1Pi deficiency is found in perhaps 1% of patients with clinically significant emphysema. These patients have inherited two so-called Z genes in this highly polymorphic (more than 30 alleles have been described), autosomal codominant system. The PiZ phenotype is seen about once in every 2,000 births in populations of northern European origin. Circulating levels of α_1Pi are reduced to about 15% of those seen in the 95% of persons with the common or so-called PiM phenotype.

Normal and abnormal α_1-protease inhibitors have been synthesized through recombinant DNA and other methods. Therapeutic quantities are being prepared by plasma protein fractionation, and this product has been released as an orphan drug. Plasma levels of α_1Pi can be restored to presumably protective concentrations by weekly intravenous doses of 60 mg per kg of body weight. It is a safe agent as judged by year-long trials in a few patients.

Studies to show long-term clinical effects have not been done; indications for its use are not defined. Initiating therapy early in life is unreasonable because not all with the PiZ phenotype will have clinically significant lung disease. In end-stage disease, correcting a protease-antiprotease imbalance could not reverse severe lung damage. Clinical judgment, therefore, dictates using the drug in patients with early but definite signs of lung injury. There are theoretic reasons to implicate a protease-antiprotease imbalance in other forms of emphysema, but replacement therapy should be restricted to use in those with severe deficiency.

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Radiologic Diagnosis—Chest Imaging

RADIOLOGIC DIAGNOSIS in chest medicine continues to be based on the "plain film," or a routine radiograph. Tomography of the mediastinum and lungs has been almost entirely replaced by computed tomography (CT). While most commonly used to screen the mediastinum for enlarged lymph nodes in the staging of lung cancer, CT is nearly ideal for distinguishing vascular structures from other structures or masses in the mediastinum. The requirement for intravenously administered contrast material is a modest limitation, though this causes all of the nonradiologic hazard of the procedure. Magnetic resonance imaging (MRI) in the chest offers less geometric resolution than CT but does not require contrast material to identify blood vessels. Though it is a new and expensive modality, MRI is already established as the safest and most versatile way to image vascular structures. It has the advantage in certain cases of forming clear images in other planes, such as sagittal and coronal, in addition to the transverse plane used by CT.

The most recently accepted technique for imaging the lungs is high-resolution CT. If the x-ray beam is narrowed to

only 1.5 to 2.0 mm, compared with the conventional 10.0 mm, the "slice" will show much less volume averaging or blurring of adjacent structures. An edge-enhancing algorithm in the computer helps sharpen the margins of vessels and bronchi. The highest resolution is then obtained by restricting the field of view, which magnifies the image. This technique provides anatomic detail comparable to a naked-eye view of a section of tissue. Details of miliary disease, lymphatic spread of carcinoma, and interstitial fibrosis, for example, are more specific than on chest radiographs or conventional CT scans. Detection of bronchiectasis by CT scan, though still somewhat controversial, is clearly more reliable and convincing than with high-resolution scans. The degree to which high-resolution CT can show abnormalities when a chest film is normal, suggested in recent studies, requires further study.

Computed tomography is an ideal technique for imaging diseases of the pleural space. CT overcomes the difficulty of making radiographs tangential to the region of involvement and easily distinguishes fluid from tissue, such as tumor, fibrosis, or collapsed lung. In cases of asbestos exposure, CT is recognized as more sensitive than radiography, including oblique views, for detecting pleural plaques or in distinguishing them from extrapleural fat. Pleural calcification is much more readily detected by CT. There remains a question of the appropriateness of using this sophisticated and expensive imaging technique for screening, but it cannot be withheld when substantial compensation is at stake.

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Prolonged Outpatient Respiratory Support

PATIENTS WHO REQUIRE long-term ventilator support should be cared for in the home whenever possible. For many patients, particularly children, this provides the optimum opportunity for clinical improvement and social development. Further, it has been shown that the care of ventilator-dependent persons can be provided more economically at home.

Mechanical ventilation in the home has been most successful for patients with ventilatory failure due to neuromuscular disease; a small group of patients with severe, stable, chronic lung disease, however, may be successfully managed at home. Patients selected for home mechanical ventilatory support should require no major diagnostic or therapeutic intervention within 30 days of discharge. Blood oxygen tension should be greater than 60 mm of mercury on a fraction of inspired oxygen of less than 40%. Wide fluctuations in arterial oxygen and carbon dioxide tensions should not occur. Patients, except for those managed with negative-pressure ventilators, should have a secure tracheostomy and an active cough and gag reflex and should not require frequent suctioning. They should be free of infection, and medical problems should be stable. They must express a desire to be discharged to home and cooperate in learning the skills required of a ventilator-assisted patient.

Caregivers must be found who have the physical, emotional, and cognitive abilities required to meet the needs of a ventilator-assisted patient. A suitable, safe home environment is necessary, with sufficient space and adequate electrical requirements and a backup power supply.

There must be a primary care physician, medical and pharmaceutical suppliers, a home health agency, and an emergency support system. Sufficient financial resources must be available to cover the total costs of environmental modification, equipment, supplies, and paid caregivers.

Before discharging a ventilator-assisted patient, a thorough evaluation of the patient and resources is done by a skilled team. If the patient and resources are appropriate, an intensive program tailored to the individual patient's needs is initiated. The patient and caregivers are required to show they are able to do all needed care safely outside the hospital environment.

Appropriate arrangements are made with community health agencies, durable medical equipment vendors, and state and local agencies, including the phone company, utility company, fire department, and emergency medical services.

Although a time-consuming process, discharging ventilator-assisted patients is feasible, practical, and rewarding for patients, their families, and the medical team.

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Nutritional Support of Patients With Chronic Lung Disease

PATIENTS WITH CHRONIC obstructive pulmonary disease (COPD), particularly those with moderate to severe impairment of lung function, are often undernourished. A number of studies have documented a correlation between a decrease in the one-second forced expiratory volume and a decrease in body weight, particularly in patients with emphysema. This often occurs despite a seemingly adequate caloric intake and has been attributed to an increased energy expenditure caused by the increased work of breathing.

Experimental malnutrition has produced a number of effects on the respiratory system, including a blunted ventilatory response to hypoxia and a delayed clearance of lung bacteria. In addition, necropsy studies on underweight patients show that the muscle mass of the diaphragm is decreased. The potential clinical consequences of these findings are evident and include an increased incidence of pneumonia, atelectasis, impaired cough, altered gas exchange, and respiratory failure. Patients with emphysema and weight loss also have an increased mortality rate.

These findings prompt clinicians to institute vigorous nutritional therapy in patients with moderate to severe COPD, although scientific evidence confirming the benefits is sketchy. Nutritional therapy can improve a patient's nutritional status, but the documentation that it can improve lung function or clinical outcome is limited at present. Nutritional therapy for ventilator-dependent patients has been shown to

increase the likelihood of successful weaning, but the effects of nutritional therapy on stable patients with COPD are less clear and are under investigation. A recent preliminary report, however, showed that three months of supplemental oral nutrition in poorly nourished COPD patients resulted in decreased breathlessness and increased muscle strength, walking distance, and general well-being. Other studies in malnourished patients with emphysema have shown an improvement in respiratory muscle function after nutritional intervention. Considering the chronic nature of this disease, it is not surprising that nutritional therapy may have only a limited impact. Regardless, malnutrition can be an additive factor to morbidity and perhaps to mortality in this disease, and thus prompts our concern and attention.

The care of patients with COPD should include a careful nutritional assessment and intervention where necessary, particularly in patients with chronic bronchitis and emphysema in whom malnutrition is more prevalent. Patients with severe lung impairment who are underweight may need a higher caloric intake than expected. Standard formulas for predicting energy expenditure often underestimate their needs. Recent work indicates that the Quebbeman-Ausman predictive equation correlates well with indirect calorimetry in patients with COPD (for men, daily caloric requirement = weight $\times$ 12.3 + 754; women, weight $\times$ 6.9 + 874; weight in kg). This may require using liquid dietary supplements, including tube feedings for inpatients whose dietary intake may be inadequate. Overfeeding must likewise be avoided because of its obvious consequences. If a patient with severe pulmonary impairment has hypercapnia, care should be taken to avoid a high-carbohydrate nutritional intake that can increase carbon dioxide production and worsen the hypercapnia in these patients. A special liquid formula is available for this use.

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Newer Methods in Sleep Disorders Medicine

SLEEP DISORDERS MEDICINE is a new clinical area dealing with disorders such as the sleep apnea syndrome, periodic leg movements of sleep, narcolepsy, insomnias, and the assessment of impotence. A diagnosis relies on a history and physical examination and also on the ability to record both nocturnal sleep and daytime sleep tendencies. Polysomnography, the laboratory-based recording of sleep, typically includes monitoring an electroencephalogram (EEG), electro-oculogram, and electromyogram to score sleep stages. Additional variables recorded for diagnostic purposes may include respiratory effort and airflow, oxyhemoglobin levels (oximetry), an electrocardiogram, or penile tumescence. Laboratory-based polysomnography also involves simultaneous monitoring by a technician of patient activities and equipment, videotaping for later review, and direct correlation with patient expectations and experiences. Understandably, this is labor-intensive and expensive.

Recent technical advances have allowed for easier and more accurate characterization of certain sleep-related variables. The use of microprocessors has greatly aided the ability to store and analyze data. Computerized programs are available to analyze continuous oximetric data. The programs provide graphic results and an immediate analysis of the number, length, and severity of desaturation events. This technology can be used to screen for sleep apnea and has been particularly useful in the inpatient setting. Computerized analysis of RR-interval variation can also screen for sleep apnea, indicating the severity of cardiac consequences of obstructive apnea. Computer-assisted EEG analysis and sleep stage scoring systems have become commercially available. In theory, these systems provide for efficient storage of information and use of technicians' time. Their cost-effectiveness and usefulness in clinics with various staffing and case-load requirements is not yet certain, however. Using this technology can aid traditional polysomnography and, coupled with daytime alertness testing, allow for an accurate diagnosis, estimation of the severity of a disorder, the impact of abnormal physiologic variables on cardiovascular and neuropsychologic function, and the determination of treatment.

Ambulatory monitoring is becoming more sophisticated, reflecting a need for accurate and inexpensive diagnostic methods. Sleep disorders are common, and large populations that may be undiagnosed, such as hypertensive men who snore, can benefit from widespread screening. Portable systems can be used to diagnose sleep apnea or the periodic leg movements of sleep, but patients whose results show abnormalities often require polysomnography to determine a specific treatment, thus increasing the cost in certain cases.

As microprocessing techniques improve, more physiologic variables can be recorded in the home. For example, several channels of an EEG can be recorded on a cassette tape to detect seizure foci. The wrist movement monitor is a simple method of differentiating wakefulness from sleep and has been validated in clinical studies. Analog or digital techniques can be used to record respiratory effort, electrocardiograms, and movements of the wrist or legs. Although available, home monitoring of oximetry is not widely used but in combination with respiratory measures can add diagnostic certainty. Using microprocessors to evaluate nocturnal penile tumescence holds a future promise for home diagnosis, but this technology is not fully validated. These devices may be best used in combination with laboratory observation to show the association of erections with rapid-eye-movement sleep, to involve the patient in an objective assessment, and to rule out sleep disorders that can themselves cause impotence.

Sleep disorders medicine is a rapidly changing discipline that requires prolonged monitoring of many physiologic variables. In addition to technical advances, clinical decision analyses are evolving to help physicians manage and advise patients who are too sleepy to safely perform activities such as driving a car or working in industry.

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Pulmonary Complications of the Acquired Immunodeficiency Syndrome

PULMONARY COMPLICATIONS are a major source of morbidity and mortality in patients with the acquired immunodeficiency syndrome (AIDS). Indeed, a sudden increase in the prevalence of *Pneumocystis carinii* pneumonia in otherwise healthy young homosexual men first alerted the medical community to this disease. The T-cell defect produced by the human immunodeficiency virus leaves these patients prey to numerous opportunistic pathogens and neoplasms that produce pulmonary disease.

Pneumocystis carinii is the major pulmonary pathogen occurring in 60% to 85% of patients with AIDS. The presenting symptoms include fever, cough, and dyspnea (85%), with chills (26%) and pleuritic chest pain (23%) occurring less frequently. A chest x-ray film is usually normal or shows diffuse interstitial infiltrates. Unilateral infiltrates and cavitary disease have been reported in patients with *P carinii* pneumonia. The alveolar-arterial oxygen difference is typically widened—> 15 torr, 92%—and portends a poor prognosis if greater than 25 torr. Although gallium lung scanning, the diffusing capacity for carbon monoxide, and exercise testing may be used for noninvasive assessments, a diagnosis rests on detecting organisms. Tests of induced sputum specimens may be positive 50% of the time, and transbronchial lung biopsy combined with bronchoalveolar lavage has a 95% to 100% sensitivity. Pentamidine isethionate or trimethoprim-sulfamethoxazole, administered intravenously for two to three weeks, remains the mainstay of therapy. Prophylactic studies using nebulized pentamidine aerosol delivered into the bronchial tree are very encouraging. A 15% to 30% mortality is expected with each episode of *P carinii* pneumonia, however.

Other pulmonary infections associated with AIDS include *Cytomegalovirus* (15% to 34%), *Mycobacterium avium-intracellulare* (16% to 21%), *Mycobacterium tuberculosis* (4%), fungal infections (4%), and, most particularly, cryptococcal pneumonia, *Legionella pneumophila* (4%), and *Nocardia*. Because of a B-cell defect, AIDS patients also have a higher incidence of bacterial pneumonias (10%), chiefly caused by *Staphylococcus aureus*, primarily in association with pulmonary Kaposi's sarcoma.

There are also noninfectious causes of pulmonary infiltrates in this patient population. Kaposi's sarcoma is clinically and radiologically indistinguishable from *P carinii* pneumonia and accounts for about 10% of infiltrates. Pulmonary Kaposi's sarcoma is associated with a high mortality rate—88%. Nonspecific pneumonitis, on the other hand, generally carries a good prognosis and may be responsible for as high as 12% of the complications of AIDS.

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Editorials

Can Any Good Come From AIDS?

THE FULL IMPACT of the acquired immunodeficiency syndrome (AIDS) epidemic has yet to be felt, even among those most at risk. The disease is lethal, it is clearly spreading, and medical science has not yet found a scientific way to prevent or cure it. There already is significant impact. Where the prevalence is high, there is evidence of serious strain on both the health care system and on traditional cultural mores. It is all too clear that these stresses are likely to bring about unprecedented changes in health care and in society that now can only be imagined. Human behavior and the methods of spread of the disease being what they are, these changes will be local, national, and even worldwide. If the epidemiologic predictions are anything like borne out, human suffering, mortality, and just plain costs will be staggering.

Can some good possibly come from this AIDS epidemic? It seems that some already has. For example, basic biomedical research is receiving more support in the hope that it might lead to better prevention and cure. The Food and Drug Administration has been persuaded to speed up its drug approval process to enable AIDS victims to take a chance on possible amelioration or cure with experimental drugs, with full realization that the safety and efficacy of such drugs might not yet be established. This was something long overdue, even before the AIDS epidemic.

As the AIDS pandemic spreads, there certainly will be other consequences. A new openness and objectivity about sexual practices is already evident. There is new attention being paid to the scourge of drug abuse and its possible role in spreading the disease. New efforts to control sexually transmitted diseases are riding on the coattails of the AIDS epidemic. And if significant changes in sexual practices come about because of the fear of AIDS, a welcome byproduct could be some significant reduction in the number of unwanted pregnancies, particularly among teenagers and perhaps even among drug abusers. In some communities there are already measurable trends toward safer sexual practices among gay men.

A rising caseload of patients will place serious stress on the health care system. One can safely predict that when some critical point is reached, the health care resources, monetary and other, will fall significantly short of what is needed, with serious social, economic, and political consequences, first in the community, and then, as things get worse, in the nation and perhaps even in the world. Could any good possibly come of this? In this nation, at least, the health care system already falls short of what is needed, even without the AIDS epidemic, if one considers that 30 or 40 million people have no health insurance at all, and, therefore, have limited access to the system. Nor can our system be considered economically efficient or friction-free. Quite the opposite. Its performance is severely hampered by flawed economic theories and bumbling interventions by government. It is now fettered, restrained and held down by high administrative overhead costs, excessive regulation, costly litigiousness, and well-intended but often ill-informed intrusions into medical practice from government and the private sector. More recently, the health care system is being leeched to provide profits for private investors, diverting funds from needed patient care. It will take an enormously powerful force to shake all this unwanted baggage loose and make more streamlined health care available to the growing numbers who need it. Will AIDS prove to be this force, a force strong enough to cut through and reduce the wasteful impediments that in many ways tie the hands of the health care system?

There is yet another dimension. We all live in one world and people move about in it sharing cultures and lifestyles—and spreading AIDS. As AIDS spreads, some commonalities among humans the world over will become more evident. Already, it has been recognized that control of this disease will have to be a worldwide effort, and remarkably quickly, a vigorous worldwide Special Programme on AIDS has been established by the World Health Organization in Geneva. It is quite possible that the AIDS epidemic will open new channels for international understanding and cooperation that could later address other worldwide risk factors affecting human health and well being.

One can only conclude that at least some good can come from the AIDS epidemic, terrible and terrifying as it surely is. MSMW

Ruling Out Myocardial Infarction—Updating a Good Idea

WHEN CORONARY CARE UNITS were first devised, the goal was to provide an isolated area of the hospital where patients with definite acute myocardial infarctions could have ready access to the newly developed techniques of continuous electrocardiographic monitoring and direct current defibrillation.[1] Testimony to their initial success was in the form of case reports of patients who were successfully resuscitated from what previously would have been fatal ventricular fibrillation.

Within several years, coronary care units assumed an additional purpose: to prevent ventricular fibrillation with the intravenous administration of medications.[2] Once again, the influential literature was principally in the form of uncontrolled observations.

Both the concept of treating ventricular fibrillation and that of preventing it were initially applied to patients who were admitted with clear-cut signs of acute myocardial infarction. The concept that intensive coronary care might be beneficial, even if not truly cost-effective, for patients in whom there was only a suspicion of acute myocardial infarction was never subjected to even a basic level of inquiry. Nevertheless, by the early 1970s, many coronary care units reported that only about 50% of patients had acute myocardial infarctions, and, subsequently, as documented by Murata elsewhere in this issue, this level has fallen to about 30%.

Coincident with this phenomenon, a new term was coined: rule out myocardial infarction (ROMI). The ROMI patient has a clinical history or an electrocardiogram result that warrants a finite suspicion of acute myocardial infarction; further testing is required to establish or exclude the diagnosis. Because such patients also have a finite probability of acute life-threatening complications, such as ventricular fibrillation, if they are having myocardial infarctions, the coronary care unit, which was initially intended to provide

intensive therapeutic care to very high-risk patients, has evolved into a diagnostic unit for oftentimes well patients.

I would suggest that it is time for a fundamental reconsideration of the entire concept of ROMI. This reconsideration can focus on two discrete issues: how does one decide whether (and where) to admit a patient who might conceivably be having an acute myocardial infarction, and what is the purpose of the hospital admission?

I agree with Murata's conclusion that the two British randomized control trials[3,4] are not adequate to prove "no benefit" from coronary care for patients who have definite acute myocardial infarctions. In fact, our recent data[5] indicate that myocardial infarction patients who are mistakenly sent home from the emergency department have twice the mortality rate of patients who are appropriately admitted. These findings document that sending home a patient with undiagnosed myocardial infarction is actually much more risky than we had assumed in our earlier cost-effectiveness calculations.[6]

The decision on whether or not to admit a patient to hospital requires a reasonably accurate assessment of the patient's probability of acute myocardial infarction[7-9] and an appreciation of the appropriate threshold probabilities that can guide the cost-effective use of various hospital resources.[6] For patients whose probabilities of acute myocardial infarction are sufficiently high—above about 5%—to warrant in-hospital care but not high enough to warrant intensive care, my colleagues and I have proposed more routine use of initial triage to a "stepdown" or intermediate care unit.[6] Admission to a coronary care unit is not as cost-effective as most accepted medical interventions until the probability of acute myocardial infarction is at least about 15%.

Intermediate or stepdown units should provide continuous electrocardiographic monitoring and ready access to resuscitative facilities. They can be current units to which patients are commonly transferred for continued observation after an acute myocardial infarction, or they can be constructed as short-stay units in or adjacent to an emergency department. The concept is to provide the two services—monitoring and resuscitation—that were the original rationales for coronary care, without the other expensive aspects that have subsequently been added to a modern intensive care unit. The Brigham and Women's Hospital's prototypical unit has electrocardiographic monitoring, but its nursing staffing and other costs are comparable to a routine medical floor.

Suggestions about appropriate triage options based on the probabilities and thresholds for acute myocardial infarction should not obscure the rational use of the hospital for patients in whom acute myocardial infarction is very unlikely but in whom unstable angina, either of new onset or of a worsening pattern of chronic angina, is a likely diagnosis. Although the likelihood of severe, unexpected, life-threatening complications that will not permit transfer to a coronary care unit is very low if such patients do not progress to acute myocardial infarction, they nevertheless can benefit from the therapeutic interventions that can more safely be conducted in hospital than in an ambulatory setting.

For the patient with a clear-cut acute myocardial infarction on presentation, the goal of admitting to hospital is to institute appropriate therapy, sometimes including aggressive interventions such as thrombolysis. After the acute episode has been treated, attention will turn to estimating the longer term prognosis and, in high-risk patients, instituting appropriate interventions designed to improve that prognosis.[10]

The time required to rule out a myocardial infarction in a patient without a clear-cut infarction on presentation will usually be no more than 24 hours.[11] In patients who are having recurrent chest pain, however, longer periods of observation are necessary, and predischarge evaluation of the patient's functional capacity will usually be mandatory.

If a patient is admitted to rule out myocardial infarction and the infarction is ruled in, the postdiagnosis goals are the same as for a patient who presented with a clear-cut myocardial infarction. If, however, the diagnosis of myocardial infarction is excluded, the physician's diagnostic responsibility has not ended, as the absence of acute myocardial infarction does not exclude the possibility of unstable angina or of other important conditions. One of the most prevalent errors I have seen is the tendency for some physicians to assume that the admission diagnosis of ROMI implies that a patient is appropriate for discharge when the rule out has been accomplished. Before a patient can be considered appropriate for discharge, further diagnostic tests, such as exercise tolerance testing, should commonly be done to document that discharge is safe. Even though the exercise test is not a perfect discriminator of the presence or absence of coronary artery disease, exercise electrocardiography or exercise thallium scintigraphy are reasonably reliable maneuvers for estimating the prognosis, and especially the safety of hospital discharge, with the option of further evaluation after discharge.[10,12,13]

Schroeder and colleagues have shown that the long-term prognosis in patients who are admitted to hospital with angina but no infarction is equivalent to that in patients with infarction.[14] Thus, from the standpoint of a long-term prognosis, ruling out a myocardial infarction is not nearly as important as establishing the presence or absence of unstable ischemic heart disease. In contrast, the distinction between the presence or absence of acute myocardial infarction is very important from the standpoint of the cost-effectiveness of the initial triage decision.

To answer Murata's question regarding evaluating a patient who arrives at an emergency department with chest pain, I think that it really is worth the effort to rule out myocardial infarction in the coronary care unit if a patient has a high probability of acute myocardial infarction. If the probability is about 5% to 15%, however, the same *diagnostic* goal can be better achieved in the setting of a stepdown unit or intermediate care unit. Regardless of where a patient is located, the ruling in of a myocardial infarction should stimulate a series of maneuvers that are designed to minimize short-term morbidity and mortality, to estimate long-term prognosis, and to alter it, if possible. Regardless of where a myocardial infarction is ruled out, the physician must pursue an alternate diagnosis, including efforts to evaluate the possibility of unstable angina, and be sure that the patient's condition is sufficiently stable before discharge.

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Intensive Control Measures for Streptococcal Infections—Is There a Need?

SINCE REBECCA LANCEFIELD FIRST IMPLICATED the group A *Streptococcus* in the pathogenesis of rheumatic fever, and Denny and co-workers showed that the disease could be prevented through adequate treatment of the preceding streptococcal pharyngitis,[1] we have sought more effective means of applying this knowledge to decrease the incidence of this life-threatening sequela of an exceedingly common infection. Unfortunately, this has not been as easy a task as it might seem since streptococci present us with several problems that make control difficult. First, there is clearly no means of establishing a diagnosis of streptococcal pharyngeal infection without the use of a culture or a positive rapid antigen test (a negative test does not rule out infection and, therefore, should always be confirmed with a culture). Second, the organisms, on occasion, may assume less than characteristic features, making them hard to identify without the use of selective or enriched media, subculture, and serologic identification. Third, strains associated with the development of acute rheumatic fever often do not produce significant symptoms during the acute stages of infection. This has led a number of workers to devise, apply, and attempt to evaluate more intensive control measures like those described by Phibbs and associates elsewhere in this issue.

I greatly enjoyed the opportunity to read this article, as it brought back fond memories of the two years I spent as an Epidemic Intelligence Service officer assigned to the Streptococcal Disease Section of the Ecological Investigations Program in Fort Collins, Colorado. It was during that time that I first met Dr Phibbs and had the opportunity to see firsthand the intensive control program in Casper, Wyoming (and to fish some of the great trout streams in the Bighorn Mountains of northern Wyoming with him). There was almost a religious fervor among the health care workers and the residents of this community about the streptococcal control program. Clearly, if it accomplished nothing else, it made the citizens aware of the problem of streptococcal infections and rheumatic fever. It probably also improved the diagnosis and management of acute streptococcal infections by the physicians of Natrona County and the state of Wyoming as a whole because cultures and adequate therapy were mandated before children could reenter school. According to data reviewed in the current article, the intensive program in Casper decreased the isolation rate of group A streptococci among schoolchildren to exceedingly low levels (1.3%). Furthermore, similar programs have resulted in profoundly lower isolation rates in other areas of the country.

The major question, however, is whether such an intensive, time-consuming, and, therefore, expensive program actually decreased the incidence of rheumatic fever and rheumatic heart disease. The data clearly demonstrating such a decrease are difficult to obtain. Phibbs cites evidence of fewer cases of acute rheumatic fever occurring among schoolchildren (N = 4) versus non-schoolchildren (N = 25) in the 1957 to 1959 outbreak in Natrona County. Unfortunately, no denominators for the groups are given in order that attack rates can be calculated. While 4 versus 25 cases certainly seems impressively different, we simply have to know what the total population at risk in each group is before valid conclusions can be drawn.

Another bothersome question is raised by the data cited above. Did the control program in any way contribute to disease development in the non-school population? Were the children in this group ones who had previously been in school and, therefore, had little prior exposure to streptococci that would result in the development of protective immunity? As indicated by Phibbs and associates, our group from Fort Collins surveyed the levels of protective-type specific M-protein antibodies in the Casper schoolchildren and found them to be lower than in children from areas without such a control program. This certainly could indicate less exposure to group A streptococci or more rapid therapy, which would be expected to blunt the immunologic response. It also indicates that the schoolchildren in Casper had less protective immunity to the common M-types of streptococci. Would streptococcal infections, rheumatic fever, and rheumatic heart disease more likely develop in these children when they were removed from the control program? We really need these data in order to be able to adequately assess such intensive control programs.

The lack of cases of acute rheumatic fever in 1978, cited by Phibbs, among the 13,000 members of the Papago tribe in Arizona after an average of 6 cases per year is also impressive. This may well be related to the institution of the control program as suggested by the authors. The incidence of acute rheumatic fever in the rest of the country was plummeting during this time period, however, with most rates being less than 1 per 100,000 population. A rate anywhere near this low would result in no cases among the 13,000 tribe members of all ages in 1978. What has happened to the incidence of acute rheumatic fever in that population since 1978?

There is a second reason for caution in interpreting these data; elaborate control measures or even the planning of such measures is notorious for decreasing the incidence of infectious diseases in a given situation. This was clearly demonstrated to me during my fellowship at the University of Minnesota when an intensive program was put into effect to

determine if penicillin could prevent the development of nephritis in an isolated population which had previously had a high incidence of this poststreptococcal sequela. Nephritis promptly disappeared from the entire population, completely negating the entire two-year study. Similarly, the mere holding of a planning meeting to study the outbreak of acute rheumatic fever in the intermountain area surrounding Salt Lake City "resulted" in the disappearance of cases for three months.[2] Almost all epidemiologic investigators have experienced similar occurrences.

Taking into consideration these concerns about the institution and evaluation of intensive group A streptococcal control programs, I have to say that I think there are instances where these may be of value. Furthermore, Phibbs and colleagues have been bold and persistent in developing and carrying out such control programs. Preventing even one case of serious rheumatic heart disease in a young person is worth a great deal of effort, in my opinion. There is little doubt in my mind that many more cases can be prevented in certain circumstances through the educational effects of such an intensive program alone.

What constitutes the set of circumstances that indicates the need for instituting an intensive program of group A streptococcal control? Large, documented outbreaks of acute group A streptococcal disease are clearly an indication. A classic example of such an outbreak occurred at the United States Air Force Academy in the spring of 1968.[3] Approximately 1,200 cadets were examined and treated for streptococcal pharyngitis over a five-day period following the ingestion of what was probably a contaminated tuna salad. The remainder of the 2,000 cadets were promptly treated with the intramuscular administration of long-acting penicillin or given erythromycin by mouth; no cases of poststreptococcal sequela occurred.

Intensive programs like that described by Phibbs and colleagues might be indicated in relatively isolated communities in which several cases of acute rheumatic fever have occurred. These clusters of cases may be associated with an increase in the prevalence of group A disease and carriage in the population and an increase in the percent of strains that are M-typeable. An intensive program of culturing and treatment like that described by Phibbs would seem to be indicated under these circumstances.

Should such an intensive program be applied to larger populations experiencing a high incidence of acute rheumatic fever? A resurgence of the disease has occurred in the intermountain area surrounding Salt Lake City during the past three years.[2] We have now documented about 150 cases of the disease.[4] The attack rate among 5- to 17-year-olds in Salt Lake County in 1985 was 18 per 100,000, which is tenfold higher than any rate reported since 1982.[2] A particularly distressing aspect of the current outbreak is the fact that more than two thirds of the patients we saw said they had not had symptoms of respiratory illness in the two months before the onset of acute rheumatic fever. Thus, most patients, including physicians' children, never sought medical attention. These patients would likely not have been picked up by screening of symptomatic school children like that used in Natrona County. Perhaps the random culturing of classroom rows would have detected some of these patients, or an overall increase in streptococcal carriage would have alerted health care personnel to the problem. Surveys of Utah schoolchildren by our group, however, at the peak of the outbreak did not reveal a particularly high group A streptococcal carriage rate (about 15%). The detection of mucoid-appearing M type 3 and 18 strains in patients and their siblings and classmates was probably more significant than the overall rate of streptococcal infection. Of interest are reports of additional outbreaks of acute rheumatic fever in Ohio and Pennsylvania associated with similar mucoid strains.[5-7]

Clearly we need to determine why and how a particular group A streptococcal strain produces rheumatic fever in a given person. Using new techniques in molecular biology, protein chemistry, and immunology, we may be on the threshold of being able to do this. For instance, Zabriskie and colleagues have developed a monoclonal antibody that is capable of detecting an alloantigen on the B cells of essentially 100% of patients in whom acute rheumatic fever develops.[8] Thus, it may be possible in the near future to identify those persons at risk for the disease and thereby concentrate most of our efforts at control on these patients. Alternatively, the factor(s) that make a particular strain "rheumatogenic" may be determined, thus allowing us to concentrate on the detection and treatment of infections due to these streptococci. We could also target these strains in attempts to produce effective vaccines against the acute infection. Unfortunately, from our recent experience, it appears that federal funding agencies are much more interested in developing artificial hearts than in studying the microbiologic, immunologic, and genetic mechanisms involved in the pathogenesis of the leading cause of acquired heart disease in young people in the world. Until priorities are changed, we will go on constructing unusual replacement machines for already damaged hearts of older citizens rather than deciphering the key questions remaining about acute rheumatic fever and rheumatic heart disease. Should the resurgence of acute rheumatic fever continue in the United States, as it apparently is, then there may well be need for the type of control programs recommended by Phibbs and colleagues.

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Acute Myocardial Infarction Following a Gila Monster *(Heloderma suspectum cinctum)* Bite

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ACUTE MYOCARDIAL INJURY following animal venom injection has been reported in the literature.[1-3] Brown and Dewar described a case of myocardial infarction after *Vipera berus* (European viper or common adder) bite.[1] They postulated that infarction resulted from arterial thrombosis due to severe hypotension. Askanas implicated a similar mechanism in a case of posterior myocardial infarction after a snakebite.[2] Aravanis and co-workers also described a case of myocardial infarction after a viper bite[3] and suggested this was a direct cardiotoxic effect of the venom.

We report the first recorded case of acute myocardial infarction following the bite of a banded Gila monster *(Heloderma suspectum cinctum)* in a previously healthy young man. The clinical history and the biochemical data available suggest that mechanisms different from those previously suggested were likely involved.

Report of a Case

The patient, a 23-year-old male herpetologist, was bitten by a banded Gila monster on his left forearm after the animal was captured near Lake Mead in Nevada. The animal's jaws were immediately pried open using two pieces of iron as levers. The total bite exposure time was about 1½ minutes. The patient reached the University Medical Center of Southern Nevada in Las Vegas two hours after the bite.

On initial physical examination in the emergency department, the young man was awake, oriented, and complaining of dizziness and left forearm pain. His blood pressure was 76/54 mm of mercury, his pulse rate was 140 beats per minute, and respirations were 18 per minute. The heart and lungs were normal to auscultation. Inspection of the bite wound showed a circle, 4 cm in diameter, formed by 12 teeth marks. The area of the bite was very tender and indurated with a surrounding area of erythema and edema. The patient did not have chest discomfort or shortness of breath.

He was immediately placed in Trendelenburg's position and intravenous infusions of 1,000 ml of normal saline and 250 ml of 5% dextrose in water were started at full flow. An electrocardiogram was done and showed a right bundle branch block, a left posterior fascicular block, and ST-segment changes suggestive of an acute anterolateral infarct (Figure 1). Multiple ventricular premature beats were noted on the telemetry monitor, and the administration of lidocaine, 2 mg per minute after an initial bolus of 70 mg, was started. The blood pressure rose slightly with hydration, and the patient received 50 mg of diphenhydramine hydrochloride intravenously along with 0.3 ml of epinephrine subcutaneously. A Foley catheter was inserted and revealed no urine output. The patient was admitted to the intensive care unit where a dopamine infusion at 5 μg per kg per minute was started. A Swan-Ganz catheter was inserted and showed a capillary wedge pressure of 5 mm of mercury, a central venous pressure of 2 mm of mercury, a cardiac output of 10.17 liters per minute, a cardiac index of 4.99 liters per minute per m^2, and a systemic vascular resistance of 532 dynes per second per cm^{-5}.

Initial serum studies elicited the following values: leukocyte count 48,300 per μl, hemoglobin 18.6 grams per dl, platelet count 171,000 per μl; a peripheral blood smear showed moderate burr cells, few target cells, and slight anisopoikilocytosis; a prothrombin time of 17.6 seconds, partial thromboplastin time of 54 seconds, fibrinogen split products greater than 40 μg per ml, and fibrinogen level 68 mg per dl. A blood urea nitrogen level was 23 mg per dl, creatinine 3.0 mg per dl, potassium 2.7 mEq per liter, phosphorus 1.5 mg per dl, magnesium 1.1 mg per dl, and creatine kinase 4,697 IU with a positive MB band. Subsequent blood studies showed a worsening thrombocytopenia (complete results given in Table 1). An x-ray film of the left forearm showed no retained teeth.

The patient received two units of fresh frozen plasma and three more liters of fluids with electrolytes replacement before a clear yellow urine output was established two hours after admission. The patient was given 0.5 ml of tetanus toxoid intramuscularly, and a prophylactic regimen of antibiotics was started. The patient had also several episodes of vomiting. In the few hours following admission, the systemic vascular resistance improved and the cardiac rhythm reverted to a regular sinus rhythm. The administration of lidocaine and dopamine was discontinued. A significant diuresis and a reduction in his creatinine level occurred over the following few days. By the third hospital day the platelet count started to increase and the myocardial conduction abnormalities disappeared (Figure 2). The ST-segment elevation persisted throughout his stay, however. His left arm became progressively more edematous with accompanying axillary lymphadenitis. This gradually resolved over the remainder of his hospital course, which was otherwise uncomplicated.

Echocardiography done on the second hospital day was normal. A scan of the heart using technetium Tc 99m pyrophosphate was done on the third hospital day and showed increased uptake in the lateral wall of the left ventricle, a finding consistent with myocardial damage. A thallium stress test was done after his discharge and showed a sharply defined area of decreased uptake at the apex of the left ventricle during stress that does not fill in after rest. A rest-exercise isotope angiocardiogram showed a generalized left ventricular wall hypokinesis at rest, most pronounced at the apex. At peak stress, every area of the heart increased vigorously in contractility except the apex, which remained hypocontrac-

(Bou-Abboud CF, Kardassakis DG: Acute myocardial infarction following a Gila monster *[Heloderma suspectum cinctum]* bite. West J Med 1988 May; 148:577-579)

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tile, consistent with a scar from a prior myocardial infarction.

The patient gave no history of any cardiac risk factors but admitted that he had used cocaine heavily a year before this admission. He said there was no recent usage. The patient was feeling well after discharge and refused cardiac catheterization. Follow-up electrocardiograms showed disappearance of the ST-segment elevations and the development of T-wave inversion.

Discussion

The Gila monster *(H suspectum cinctum)* is a poisonous lizard found mainly in the desert areas of the southwestern United States and western Mexico. Its bite is venomous in 70% of the cases. The symptoms are usually due to the local effect of the venom: edema, tenderness, lymphangitis, and lymphadenitis. Systemic manifestations are mild and nonspecific; weakness, faintness, dizziness, and sweating are common early symptoms. Nausea, vomiting, increased perspiration, and shock are less common. Slight reversible thrombocytopenia is rare.[4] Anaphylactic shock[5] and myocardial conduction disturbance[6] have also been described.

This case of Gila monster bite presents some unusual features. There is no doubt from the electrocardiographic changes, cardiac enzyme elevations, ^{99m}Tc pyrophosphate heart scan, and the thallium stress perfusion study of the heart that an acute myocardial infarction followed the lizard's bite. The mechanisms by which this was brought about could be multiple, and there is no proof that any one of them is the major factor.

Hypotension

Though it is rare for hypotension alone to be the cause of myocardial infarction in a previously healthy young man, its severity and duration with the resultant reduced blood flow might have caused coronary arterial or arteriolar thrombosis.[1] This is even more plausible if the involved coronary artery is already stenosed by an atherosclerotic lesion. Without the findings of a cardiac catheterization, however, this remains a theoretic and remote possibility in this young man.

Direct Toxic Effect of the Venom

An intraventricular conduction defect and nonspecific T-wave changes have been previously described[6] following a Gila monster bite. There is no indication that the lizard venom has any other effect on the myocardium or the coronary vessels. Serotonin is a major constituent of the venom, however, and could produce coronary vasoconstriction, thus predisposing to myocardial damage.[4]

Intravascular Coagulopathy

There is clear-cut evidence in our case that a consumptive coagulopathy followed the Gila monster bite, as evidenced by

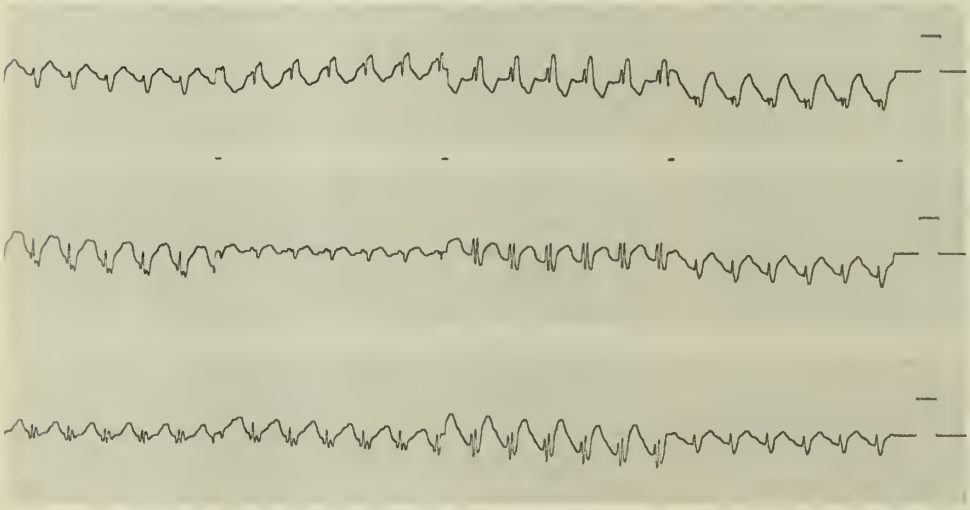

Figure 1.—A tracing of an electrocardiogram done on presentation shows evidence of an acute anterolateral infarction. Right bundle branch block and left posterior fascicular block are also present. Leads shown are **(top)** I, aV_R, V_1, and V_4; **(middle)** II, aV_L, V_2, and V_5; **(bottom)** III, aV_F, V_3, and V_6.

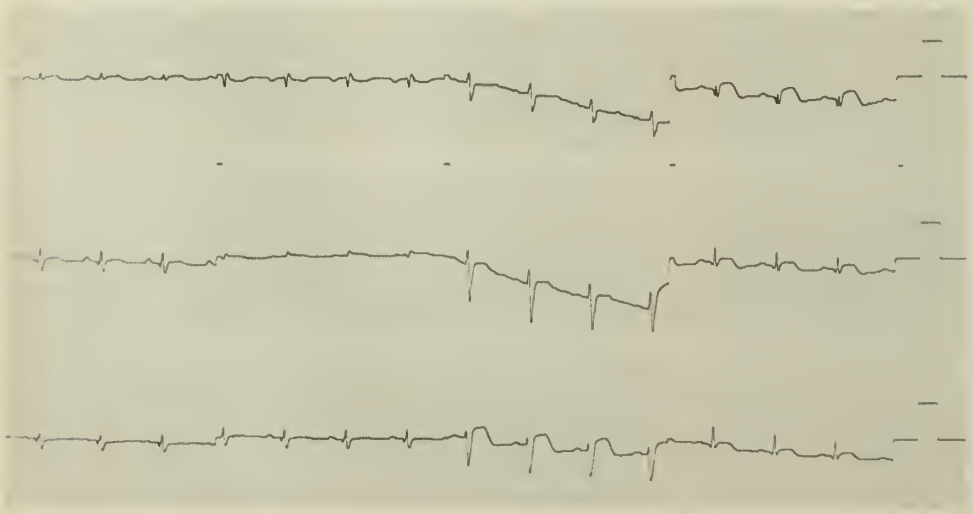

Figure 2.—After three days, the conduction abnormalities have disappeared. The ST-segment changes persist. Leads are the same as in Figure 1.

TABLE 1.—*Hematologic and Biochemical Data in a 23-Year-Old Man Bitten by a Gila Monster* (Heloderma suspectum cinctum)

Laboratory Measurement	*Hospital Day* 1	2	3	4	5	*Normal Range*
Leukocyte count/μl	48,300	25,600	15,800	12,600	13,000	4,000 to 12,000
Platelets/μl	171,000	62,000	69,000	113,000	181,000	150,000 to 450,000
Potassium, mEq/liter	2.7	3.9	4.1	3.7	4.2	3.6 to 5.6
BUN, mg/dl	23	28	19	14	15	8 to 20
Creatinine, mg/dl	3.0	2.3	1.8	1.5	1.4	0.8 to 2.0
Phosphorus, mg/dl	1.5	2.9	2.2	2.9	..	2.5 to 4.5
Magnesium, mg/dl	1.1	2.8	2.1	..	2.1	2.0 to 2.7
Prothrombin time, s	17.6	13.5	..	..	..	11.0 to 13.0
PTT, s	54	27	..	..	..	21 to 32
Fibrinogen, mg/dl	68	..	..	..	..	200 to 400
Fibrin split products, μg/ml	40	..	..	..	..	0 to 10
Creatine kinase, IU	4,697	3,965	731	432	350	37 to 374
LDH, IU	6,935	8,297	6,947	5,631	4,824	297 to 537
MB bands	Pos	Pos	Neg	Neg	Neg	

BUN=blood urea nitrogen, LDH=lactic dehydrogenase, Neg=negative, Pos=positive, PTT=partial thromboplastin time

an increase in the prothrombin time, partial thromboplastin time, and fibrin-split products, along with a decrease in the fibrinogen level and total platelet count. Patterson and Lee[7] suggested that, in vivo, the venom alters either prothrombin or one or more of the known factors—that is, V, VII, and X—involved in the conversion of prothrombin to thrombin. This conclusion was questioned by Russell and Bogert in their review.[4] To our knowledge this is the first case where a disturbance in blood coagulation was recorded in a human following the bite of *H suspectum cinctum.* Ueda and colleagues reported an association between disseminated intravascular coagulation and the occurrence of acute myocardial infarction in the aged.[8] An intracoronary thrombosis due to the intravascular coagulopathy is another possible explanation for the myocardial infarction our patient experienced.

Coronary Spasm

Vincent and associates found that spasm alone or spasm-induced coronary thrombosis in an anatomically normal vessel can lead to sudden total occlusion of the coronary artery and thus precipitate an acute myocardial infarction.[9] A similar event could have happened to our patient and would explain his infarction.

History of Cocaine Use

The association between recent cocaine use and myocardial infarction has been well established.[10-14] The question of whether a history of previous cocaine use would result in a higher incidence of myocardial infarction has not been addressed. Simpson and Edwards in the autopsy report of a cocaine user found evidence of chronic multifocal obstructive coronary lesions that were the result of a nonatherosclerotic intimal proliferation of smooth-muscle cells with and without the deposition of collagen and elastin.[14] Similar anatomic stenoses, if present in our patient, could have made it easier for each of the above discussed factors to precipitate an acute myocardial event.

It seems unfortunate that the patient refused cardiac catheterization, which could have shed some light on the mechanism(s) involved in his myocardial infarction. Another peculiar finding in this case was the absence of any chest discomfort. Asymptomatic myocardial infarction does occur in more than 25% of all infarct patients,[15] and the possible mechanisms have been discussed by Droste and Roskamm.[16] The most likely mechanism in our patient, however, would be an inhibition of pain transmission at the spinal cord level by a high input of pain signals from the left upper extremity, which could in part be mediated by an increase in endorphin secretion.[17]

In summary, we report a case of myocardial infarction following a Gila monster bite in a young man. No previous published record of this complication as a result of the lizard bite has been found. Although the pathogenesis remains uncertain, hypotension, toxic effects of the venom, intravascular coagulopathy, or coronary spasm could all have played a role.

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Toxic Shock Syndrome and Sinusitis—A Hidden Site of Infection

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THE TOXIC SHOCK SYNDROME is a clinical state characterized by fever, hypotension, erythroderma, and mucous membrane hyperemia with eventual desquamation and multisystem involvement. Toxin-producing staphylococcal infections have been associated with most reported cases. In children the site of infection may not be as readily apparent as in adults.

We report an unusual case of the syndrome in a 13-month-old infant in whom the focus of apparent infection was in a previously unrecognized site.

Report of a Case

A 13-month-old previously healthy female infant with Down's syndrome had fever to 39.4°C (103°F) and vomiting. The following day she was seen at an outlying emergency department where an erythematous rash and nasal congestion were noted. She was treated with a regimen of amoxicillin and decongestants. Because of persistent fever, lethargy, and watery diarrhea, she was admitted to hospital on the fourth day of illness.

On admission she appeared in a toxic condition and was lethargic and dehydrated. Her temperature was 38.3°C (101°F), heart rate 150 beats per minute, respirations 32 per minute, and blood pressure 98/64 mm of mercury. There was a diffuse, erythematous, confluent macular rash on the face, upper extremities, and trunk and scattered truncal petechiae. Her conjunctivae were hyperemic. There was a profuse cloudy nasal discharge. Peripheral perfusion was decreased.

Laboratory studies done on admission elicited the following values: hematocrit 33.6%; leukocyte count 12,300 per μl (30% polymorphonuclear leukocytes, 47% bands); platelet count 142,000 per μl; sodium 125, potassium 3.1, chloride 95, and bicarbonate 21 mEq per liter; blood urea nitrogen 29, creatinine 1.3, and calcium 7.7 mg per dl; lactic dehydrogenase 340 units per liter (normal 1 to 255); and serum aspartate and serum alanine aminotransferase 80 units per liter (normal 7 to 38). A urinalysis showed 30 mg per dl protein and 30 to 50 leukocytes per field. Cultures of specimens of blood, urine, cerebrospinal fluid, stool, conjunctiva, and nasal discharge were taken before intravenous therapy with cefuroxime sodium, 100 mg per kg of body weight per day, was started.

Within the next 12 hours the patient became more lethargic and tachypneic, and metabolic acidosis, thrombocytopenia, and disseminated intravascular coagulation developed. An oral endotracheal tube was introduced, and she was mechanically ventilated, a central line placed, and fluid administered at 250 ml per kg per day to maintain adequate tissue perfusion. An infusion of dopamine hydrochloride, 5 μg per kg per minute; high doses of corticosteroids; and gentamicin sulfate therapy, 7.5 mg per kg per day, were added.

By the third hospital day the fever had resolved and she began to desquamate on the trunk and digits. The dopamine infusion was discontinued on the following day, and the endotracheal tube was removed on the sixth day.

A bacterial culture of purulent drainage swabbed from the area of the left inferior turbinate yielded a heavy growth of *Staphylococcus aureus* and a moderate growth of uncharacterized normal flora while a culture of a similar specimen from the right side yielded only the normal flora. A light growth of *S aureus* only was cultured from the left conjunctiva. The *S aureus* organisms had identical patterns of antimicrobial susceptibility, sensitive to β-lactam antibiotics and gentamicin. The organisms produced toxic-shock-syndrome toxin 1 (TSST-1). (The toxin assay was done by P. Schlievert, PhD, University of Minnesota-Duluth School of Medicine.) Cultures of specimens from other sites were sterile. Serologic studies excluded leptospirosis, Rocky Mountain spotted fever, *Mycoplasma*, and streptococcal infection.

Sinus x-ray films showed complete opacification of the left maxillary sinus. She was treated for 21 days with a β-lactam antibiotic. Before discharge the laboratory abnormalities had resolved. There has been no recurrence of the disease.

Discussion

The toxic shock syndrome was originally described by Todd and co-workers in 1978.[1] They described the cases of seven children with fever, multisystem failure, hypotension, and rash leading to desquamation. *Staphylococcus aureus* was found in 5/7 of the cases. Subsequent scientific and public attention was focused on the disease in the spring and summer of 1980 when an outbreak of cases in menstruating women using tampons was detected.

A significant proportion of cases of toxic shock syndrome are not related to menses. The collective experience of Reingold and associates[2] and Wiesenthal and Todd[3] suggests that any focus of staphylococcal infection can be associated with the syndrome. The infection often lacks the classic signs of inflammation despite the identification of toxin-producing *S aureus*. This incomplete response may hinder the detection of staphylococcal infections in unexpected sites. We propose that the maxillary sinuses represent such a site.

The case reported here meets all the criteria established by the Centers for Disease Control for the toxic shock syndrome, including hypotension, rash with subsequent desquamation, fever, and multisystem dysfunction.[4] The clinical impression was further supported by the isolation of an *S aureus* organism producing TSST-1.

Acute sinusitis complicates an estimated 0.5% to 5% of cases of upper respiratory tract infection. The responsible organisms contaminate the sinuses through retrograde inoculation from the posterior nasal chamber. Common pathogens include *Streptococcus pneumoniae, Hemophilus influenzae* (non-type b), and *Branhamella catarrhalis*.[5] Previous investigations have shown that maxillary sinus cultures done at the

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time of surgical drainage do not correlate with simultaneous nasal cultures.[5] To be considered pathogenic, though, organisms must be present in a surgical drainage specimen at a concentration greater than 10^4 per ml. The *S aureus* was identified in our patient from purulent nasal secretions only on the side of the sinusitis.

The role of the *S aureus* carrier in the toxic shock syndrome is incompletely understood. Jacobson and colleagues found a nasal colonization rate of 35% in asymptomatic adults screened before an elective surgical procedure[6]; 7% of these organisms produced TSST-1, yet no cases of the syndrome were encountered. Schlievert and co-workers showed that 11/22 healthy children harbored *S aureus* in their nares and that in 4/11, the organism produced TSST-1.[7] Todd and associates indicated that growth conditions in the nasopharynx allow colonization by *S aureus* but that the TSST-1 toxin produced, while antigenic, may have an altered, attenuated toxicity.[8]

Previous investigators have reported nasal cultures positive for *S aureus* in patients with toxic shock syndrome with no documented site of infection. Reingold and colleagues' series of 130 patients with a nonmenstrual form of the syndrome contained 13 persons with uncharacterized infection.[9] In three of these patients, *S aureus* was found in the nares, throat, and trachea, respectively. The experience of Buchdahl and co-workers with five children includes an 18-month-old infant with *S aureus* cultured from the nares, throat, and trachea, but without definite tracheitis.[10] De Saxe and associates reviewed the British experiencc, which included children in whom the focus of infection was not identified.[11] Sinus evaluation is not mentioned in any of these reports.

Because of the low degree of suspicion, the sinuses have not been routinely examined in cases of toxic shock. In upper respiratory tract infections, the sinuses can become contaminated by sneezing, sniffling, or blowing. Inflammation and blockage of sinus drainage can mimic closed-space systems frequently implicated in the toxic shock syndrome, such as nasal packing or tampon usage. The *S aureus* may proliferate in conjunction with other pathogens and produce significant amounts of toxin despite low bacterial counts or a lack of culture predominance. This is supported by experimental evidence evaluating in vivo and in vitro growth conditions on the production of *S aureus* protease and TSST-1. Todd and colleagues showed that the environment in focal infections—specifically not present in the nasopharynx—promotes elaboration of protease and TSST-1 and could play a critical role in inducing virulence.[8] The elaboration of a potent toxin by a small number of organisms may explain the minimal local tissue reaction commonly described.

Radiographs provide an accurate diagnosis in 75% of cases of acute sinusitis.[5] The maxillary sinus can be aspirated if the diagnosis is in doubt or if there is a failure of response to therapy. Early surgical debridement has been recommended to decrease the absorbed toxin dose in cases of toxic shock associated with postoperative wound infection.[12] In the case reported here, if an association of sinusitis with the syndrome had been suspected, a maxillary sinus aspiration could have documented the presence of the offending organism in the sinus cavity. Early maxillary sinus lavage could possibly have attenuated the clinical course by eliminating the focus of infection.

In summary, the toxic shock syndrome continues to be a rare cause of life-threatening shock in children. Classic indications of local infcction may be lacking, so a thorough search for the site of infection should includc culturc of spccimens of blood, urine, vaginal secretions, cerebrospinal fluid, and any wound or focal infection. The sinuses represent a potential site of concealed infection. In children, the classic complaints of sinusitis may be absent. We suggest that in children with the toxic shock syndrome who have no obvious focus of infection, the sinuses should be considered a possible site and radiographs or sinus aspiration be done to document their involvement.

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Lymphoma and Chylous Ascites

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CHYLOUS ASCITES is a rare clinical problem. Although recognized since the 16th century, reports in the literature have been infrequent and comprise for the most part single cases.[1,2] Most cases of chylous ascites in adult patients are caused by an underlying malignant disorder, with lymphomas representing 50% of such cases.[3]

Four patients presenting with lymphoma and chylous ascites were recently seen at the Los Angeles County-University of Southern California Medical Center over a period of three months. Our experience with this cluster of patients and the sparse number of publications concerning chylous ascites in patients with lymphoma prompted us to review the literature and develop a rational approach to this unusual clinical problem.

(Hufford S, Hu E: Lymphoma and chylous ascites. West J Med 1988 May; 148:581-583)

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ABBREVIATIONS USED IN TEXT

CT = computed tomographic
CVP = cyclophosphamide, vincristine sulfate, and prednisone
MOPP = mechlorethamine hydrochloride, vincristine sulfate, prednisone, and procarbazine hydrochloride

Reports of Cases

Case 1

The patient, a 49-year-old woman, was admitted to hospital in September 1986 with a three-month history of increasing abdominal distension and shortness of breath. On physical examination she had generalized lymphadenopathy and ascites. A left axillary lymph node biopsy was diagnostic of mixed large and small cleaved cell lymphoma. An abdominal computed tomographic (CT) scan revealed a large retroperitoneal mass and ascites. Paracentesis elicited creamy white ascitic fluid with a triglyceride level of 650 mg per dl, protein 2.9 grams per dl, and a cell count of 556 cells per dl with 99% mononuclear cells. A treatment regimen with cyclophosphamide, vincristine sulfate, and prednisone (CVP) was initiated in September 1986. When no response was seen after two months of chemotherapy, doxorubicin (Adriamycin) hydrochloride and diuretics were added to her treatment regimen, which prompted an immediate response. As of March 1987, the patient had received four cycles of cyclophosphamide, doxorubicin, vincristine, and prednisone chemotherapy and continued to be free of ascites, even though her diuretic therapy was discontinued two months earlier.

Case 2

The patient, a 67-year-old man, presented in October 1986 with complaints of abdominal distension and shortness of breath. A physical examination revealed ascites and generalized lymphadenopathy. A cervical lymph node biopsy was diagnostic of small cleaved cell lymphoma. A CT scan showed ascites and a large retroperitoneal mass. The ascitic fluid was milky white, with a triglyceride level of 1,078 mg per dl, total protein 4.2 grams per dl, and a cell count of 1,067 cells per dl with 91% mononuclear cells.

Radiation therapy directed at the retroperitoneal mass was begun in November 1986. A total of 2,000 rads was given over a four-week period. On a repeat CT scan, the ascites was unchanged, as was the retroperitoneal mass. By December 1986 chemotherapy was initiated with CVP, and symptomatic ascites was controlled with multiple therapeutic paracenteses. After completion of two cycles of CVP, however, there was still no change in the frequency of paracentesis required to control the ascites. Diuretic therapy consisting of furosemide and amiloride hydrochloride was started in January 1987, with resolution of the ascites and a resultant decrease in the patient's weight from 81 kg to 57 kg (178 lb to 126 lb) over a two-week period. The patient remained free of ascites following three cycles of CVP and continued diuretic therapy.

Case 3

The patient, a 58-year-old man, was admitted to hospital in September 1986 because of malaise and weight loss over three months. On physical examination he had generalized lymphadenopathy with hepatosplenomegaly. Mixed cellularity Hodgkin's disease was diagnosed from a cervical lymph node biopsy. A CT scan showed the presence of retroperitoneal adenopathy. Abdominal distension developed during the patient's hospital stay, and ascites was detected clinically. Paracentesis elicited cloudy fluid with a triglyceride content of 224 mg per dl, total protein 2.1 grams per dl, and a cell count of 650 cells per dl, of which 99% were mononuclear cells. In October 1986, therapy consisting of mechlorethamine hydrochloride, vincristine, prednisone, and procarbazine hydrochloride (MOPP) was given, with resolution of the chylous ascites after the first cycle. As of March 1987 the patient had completed five cycles of MOPP and remained free of ascites.

Case 4

This 60-year-old man presented in August 1986 with increasing abdominal girth and pain. A CT scan of the abdomen showed a large mesenteric mass. On an exploratory laparotomy he had bulky mesenteric adenopathy and chylous ascites. The histologic appearance of the mesenteric mass was consistent with small cleaved cell lymphoma. The ascitic fluid had a triglyceride level of 600 mg per dl, total protein 3 grams per dl, and a cell count of 950 cells per dl, with 99% mononuclear cells.

The patient underwent treatment with a regimen of methotrexate, doxorubicin, cyclophosphamide, vincristine, prednisone, and bleomycin sulfate, with immediate resolution of his symptoms and the ascites. By March 1987, the patient was no longer receiving chemotherapy and was clinically free of disease.

Discussion

Chylous ascites is a milky peritoneal effusion resulting from obstruction of lymph flow through chyle-transporting vessels. The composition of chylous ascites is similar to that of thoracic duct drainage, with a fat content greater than that of plasma and a total protein content on the average of about 3 grams per dl.[2-6] Triglyceride levels are elevated in all patients, with a cutoff arbitrarily set at 200 mg per dl in some studies.[3] Leukocyte counts in ascitic fluid are usually high, with a notable predominance of lymphocytes. All four of our patients met these criteria.

Lymphoma is a major cause of chylous ascites.[1-3,7] The mechanism would presumably relate to lymphomatous infiltration of draining lymphatics and lymphaticovenous collaterals below the diaphragm. Bulky neck and mediastinal adenopathy tends not to cause chylous ascites. Mesenteric adenopathy is much more common in non-Hodgkin's lymphomas than in Hodgkin's disease and may explain why chylous ascites is seen more frequently in patients with non-Hodgkin's lymphoma.[8] Although chylous ascites is recognized as a possible manifestation of lymphoma, the incidence is not well documented. In an abstract in 1966, Muggia and Ultmann reported an incidence of 0.7% (1 of 140) in patients with Hodgkin's disease and 6.2% (14 of 233) in patients with non-Hodgkin's lymphoma.[8]

In general, the incidence of chylous ascites from all causes is low. Press and co-workers reported only 1 case out of 11,589 patients at Massachusetts General Hospital over a five-year period.[3] Nix and colleagues reported 1 case in 187,000 patients,[2] and Kelly and Butt noted only 10 cases in 30 years at the Mayo Clinic.[7] Table 1 lists the major series of patients with chylous ascites and its causes.[1-3,7] Lymphoma, as mentioned, accounts for most of these cases.

The prognosis for patients with lymphoma and chylous ascites previously reported in the literature has been poor; even the most recent review reported long-term survival in only 2 of 13 patients treated with a variety of measures, including chemotherapy.[3]

Various approaches have been used in the management of chylous ascites (Table 2), with the most frequently studied and reported being dietary manipulation.[3,9-14] This approach is based on the difference in metabolism of medium-chain and long-chain triglycerides. Medium-chain triglycerides are hydrolyzed in the intestines, and the breakdown products pass directly into the portal circulation, bypassing the lymphatics, whereas the long-chain triglycerides are metabolized and transported as chylomicrons via the lymphatics. In several reports, there was resolution of chylous ascites with the incorporation of medium-chain triglycerides in the diet.[3,9-12] Those who respond to this treatment tend to be children with congenital or idiopathic chylous ascites, patients with chylous ascites related to surgical trauma, or those with nonmalignant causes of chylous ascites. Most patients with lymphoma treated in this manner have not benefited.

Attempts to manage chylous ascites with hyperalimentation,[15,16,18] peritoneal-venous shunting,[16] and repeated paracentesis[1-3,6,7,14,15,17,18] have been unsuccessful in cases associated with lymphoma.

TABLE 1.—*Causes of Chylous Ascites as Given in 4 Reports*

Cause	*Press et al, 1982,[3] No. (%) n=24*	*Kelley and Butt, 1960,[7] No. (%) n=71*	*Nix et al, 1957,[2] No. (%) n=9*	*Vasko and Tapper, 1967[1] No. (%) n=11*
Lymphoma	13 (54)	33 (46)	2 (22)	3 (27)
Carcinoma	8	29	1	5
Cirrhosis	1	1	1	...
Surgical trauma	1	2	...	...
Portal vein thrombosis	1	2	...	...
Other		2	5	3

TABLE 2.—*Therapy for Chylous Ascites*

Method of Treatment	*Study*
Dietary manipulation	Calabrese et al, 1977[12]; Frank et al, 1966[13]; Lewis and Storer, 1979[14]; Meinke et al, 1979[15]; Asch and Sherman, 1979[16]
Hyperalimentation	Sanchez et al, 1971[17]; Bruneau and Rubin, 1965[18]
Paracentesis	Vasko and Tapper, 1967[1]; Nix et al, 1957[2]; Press et al, 1982[3]; Hashim et al, 1964[9]; Weinstein et al, 1969[10]; Sanchez et al, 1971[17]; Herz et al, 1978[19]; Swensson et al, 1966[20]
Peritoneal-venous shunting	Vasko and Tapper, 1967[1]; Press et al, 1982[3]
Diuretic therapy and salt restriction	Press et al, 1982[3]
Chemotherapy	Press et al, 1982[3]
Radiotherapy	Nix et al, 1957[2]; Press et al, 1982[3]; Weinstein et al, 1969[10]

Diuretic therapy and salt restriction have been used infrequently in managing chylous ascites but apparently have substantially benefited some patients. In two of our patients, administering diuretics definitely aided chemotherapy in controlling the ascites.

Specific therapy for patients with lymphoma and chylous ascites lies in chemotherapy and radiotherapy. Radiotherapy has been used frequently, especially in earlier series. There was occasional resolution of ascites after radiation therapy, but no increased survival has been shown.[19,20] With the development of aggressive combination chemotherapy for treating lymphomas, responses and survival should improve in this group of patients. Our experience with a cluster of patients with lymphoma and chylous ascites, using specific antitumor chemotherapy together with diuretics and salt restriction, supports this contention. Longer follow-up and larger studies would be needed before further conclusions on survival could be made, however.

Addendum

A follow-up time of three months has passed since this article was submitted. Three patients remain free of ascites. Patient 3 appears to have a recurrence of Hodgkin's disease.

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Correspondence

AIDS, Autopsies, and Fear

To the Editor: Recent correspondence[1] concerning my essay "First Case"[2] questions the outlook of that piece and its appropriateness for a medical journal. The essay, as I stated in its first sentence, addresses fear. It is not a scientific discussion of the acquired immunodeficiency syndrome (AIDS). I have written scientific papers on AIDS, including articles on the safe performance of autopsies in cases of AIDS,[3-6] and on the ethical necessity to provide autopsies in cases of deaths from AIDS (Ratzan RM, Schneiderman H: "AIDS, Autopsies and Abandonment," submitted for publication). By contrast, in "First Case" I sought to explore the emotional realities of occupational exposure, to delineate the irrationalities that conflict with scientific data and published epidemiologic experience, and to focus on the means employed and psychological costs incurred in achieving an acceptable, professional performance despite severe anxiety. While such topics might interest others as well, physicians constituted the intended audience. As a profession, medicine has evolved away from a self-image of unemotional, detached comportment in accord with science alone and toward more recognition of the inevitability of feelings and the great desirability of dealing with them.

If "First Case" helped some health professionals to cope better with fear—whether of AIDS or of anything else—I have succeeded in my mission. I hope, along with Dr Geller, that it will not be misconstrued or misquoted as supporting the unethical refusal to provide any services, postmortem examination included, to AIDS patients.[7] Discussion of controversial issues always runs the risk of misinterpretation, but the solution is to provide clarity. Neither human weaknesses nor the fear of AIDS will evaporate, but both can be managed by explicit attention.

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Gas Gangrene or Anaerobic Cellulitis?

To the Editor: The article by Dennis Stevens and coworkers, "Spontaneous Gas Gangrene at a Site of Remote Injury—Localization Due to Circulating Antitoxin," in the February issue,[1] is a very interesting example of "spontaneous" clostridial infection. The demonstration of a rising antibody titre directed against θ-toxin provides an intriguing hypothesis for the localization of infection in this case. It is unfortunate, however, that the authors chose to characterize this infection as "gas gangrene." J. D. MacLennan, whose landmark article is their first reference,[2] clearly categorizes the spectrum of clostridial infections observed in human infection. He describes three stages of clostridial infection but points out that, in reality, a continuous spectrum is observed. Simple contamination is marked by clostridia growing with other bacteria in a wound with necrotic material present. There is no systemic reaction and the wound appears foul and dirty with a thin exudate. It is appropriately treated by debridement and local care without antibiotics. Anaerobic cellulitis, also termed gas abscess, is characterized by a local heavy clostridial growth without invasion. The wound is foul with brown, seropurulent discharge and abundant gas formation. There is little or no surrounding edema or systemic reaction. There is no muscle invasion. Anaerobic myonecrosis, also known as clostridial myonecrosis or "gas gangrene," is marked by local edema, a thin exudate, absence of white blood cells, no vascular hyperemia, and death of muscular tissue. Gas formation is usually scant. A profound systemic reaction, including tachycardia, hypotension, mental changes, and shock, follows if early aggressive treatment is not instituted. Dermal gangrene, bullae, and obvious gas are late findings.

The patient described by Stevens and colleagues had few systemic signs of infection, no muscle gangrene, abundant gas, and abundant white blood cells. This is the classic presentation of anaerobic cellulitis. It highlights the point made by MacLennan in his report that many cases of clostridial infection are not "gas gangrene" and do not require the kind of aggressive mutilating surgical treatment that true myonecrosis often demands. My personal experience includes two cases of local clostridial infection marked by abundant white blood cells and minimal systemic reaction and appropriately treated by local debridement and antibiotics. A third such case has been described to me. While antibody to the θ-toxin may well explain the findings in this case, physicians should be aware that localized clostridial soft tissue infections with an intact inflammatory response can occur primarily after injury and can be dealt with by a measured therapeutic response.

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Space Medicine Update

To the Editor: In the article on space medicine in the September 1987 issue,[1] my colleagues and I stated that the current record for continuous time in space was 236 days set by Soviet cosmonauts Kizim, Solovyov, and Atkov. Another Soviet cosmonaut, Yuri Romanenko, has shattered the old record by remaining in space for 326 days. Currently, Vladimir Titov and Musa Manarov are orbiting the earth aboard

the space station Mir. Whether they will attempt to spend an entire year in space remains to be seen.

As always, records exist to be broken.

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Medicine in the USSR

To THE EDITOR: As Russian-speaking physicians who have just returned from seven months in the Soviet Union, we read Dr Friedenberg's overview of Soviet health care[1] with great interest. While we can corroborate many of the author's observations, we think that his conclusions understate the sorry condition of Soviet medicine.

There is ample documentation in the Western literature of the USSR's rising infant[2] and overall[3] mortality rates, of the decline in spending on health care that by one estimate now amounts to just 2% of the gross national product,[4] and of the technologic backwardness that characterizes most hospitals and clinics.[4] To this we would add that dissatisfaction with the poor quality and corruption of the health care system is widespread among both patients and physicians.

While the illegal practice of payment on the side to physicians and nurses—required simply to have one's operation done or one's medication given—is so prevalent that it has recently been acknowledged in the Soviet press (*Izvestia,* Sep 24, 1987), worse yet is the fact that many people are distrustful of the system at any price, official or unofficial. Physicians themselves complain about policies that stress quantity, not quality, low prestige and pay, and lack of professional autonomy. Professional input in health policy and public health is also lacking, as may be judged by recent measures that mandate human immunodeficiency virus testing for many groups and prison terms for those who deliberately expose another to the virus (*Izvestia,* Aug 26, 1987).

We commend Dr Friedenberg on his accurate reporting of many facets of the Soviet health care system and would emphasize the abysmally low level of care that is a fact of life for Soviet citizens.

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Special Article

Guidelines for the Control of Human Immunodeficiency Virus Infection in Adolescents

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Although adolescents account for only 0.4% of reported cases of the acquired immunodeficiency syndrome (AIDS) in the United States, they are sexually active and, therefore, at risk of acquiring human immunodeficiency virus (HIV) infection. To address issues of HIV control in adolescents, we developed guidelines that emphasize education and medical care and deemphasize antibody testing. For adolescents known to be infected with HIV, we recommend no restrictions on access to educational or treatment programs except when their health providers recommend such restrictions to protect them from exposure to opportunistic infections. For adolescents of unknown antibody status with a possible previous exposure to HIV, we recommend that as long as the incidence of HIV infection and clinical AIDS remains low, there should be no restrictions on residential placements and no routine antibody testing.

(Oliva GE, Rutherford GW, Grossman M, et al: Guidelines for the control of human immunodeficiency virus infection in adolescents. West J Med 1988 May; 148:586-589)

The information and recommendations in this report were developed and compiled by the Adolescent AIDS Task Force,* a subcommittee of the Perinatal and Pediatric AIDS Advisory Committee of the Department of Public Health, City and County of San Francisco. It included representatives from the adolescent medicine divisions of the Department of Pediatrics of San Francisco General Hospital and Medical Center and the University of California, San Francisco; the Bureau of Family Health, the AIDS Office, the Bureau of Communicable Disease Control, the Division of Forensic Services, and Community Substance Abuse Services, San Francisco Department of Public Health; a community agency serving homosexual and homeless adolescents; and the National Center for Youth Law. These recommendations were developed in response to requests from juvenile justice staff and agencies involved in adolescent social services for guidelines for antibody testing and placement of youth at risk for or infected with the human immunodeficiency virus (HIV). This includes adolescents with the Centers for Disease Control (CDC)-defined acquired immunodeficiency syndrome (AIDS), those with lesser clinical manifestations of HIV infection such as AIDS-related complex (ARC), and those with asymptomatic infection.

The recommendations that follow apply to all adolescents known to be infected or at risk of being infected with HIV. They are designed to supplement previously published guidelines for the control of perinatally transmitted HIV infection[1,2] and for the education of HIV-infected children.[3-6]

*Members of the task force included Moses Grossman, MD (chair), Richard C. Brown, MD, D. Nicolette Collins, MD, Greg Day, Dennis Doyle, Dean F. Echenberg, MD, PhD, Abigail English, JD, Gregory Evans, Martha Henderson, Ruth Hughes, Barbara Moscicki, MD, Geraldine E. Oliva, MD, MPH, George W. Rutherford, MD, Pamela Sargeant, RN, MSN, Janet Shalwitz, MD, Florence M. Stroud, MN, MPH, Dennis Sweeney, and Frances Taylor, MD, MPH.

HIV Infection in Adolescents

Of the 42,354 cases of AIDS reported to the CDC through October 5, 1987, 170 occurred in persons 13 to 19 years old. This represents about 0.4% of all reported AIDS cases. The median age of these patients was 18 years, and 95% were aged 17 years or older; 42% were white, 37% black, and 19% Latino, with a male-to-female ratio of 5.3:1. They were reported from 31 states, the District of Columbia, and Puerto Rico; 19 (11%) were from California. Of the 170 adolescents with AIDS, 77 (45%) acquired HIV sexually, 62 (36%) through transfusion of infected blood or blood products, 11 (6%) through intravenous drug use, 10 (6%) either sexually or through intravenous drug use, and for 10 (6%), the route of acquisition was undetermined. Of the 170 adolescents, 21 (12%) had histories of intravenous drug use (Table 1).[7]

In San Francisco, as of the same date, there had been five cases of AIDS reported in adolescents. All were 17 years old or older, two were white, one black, and two Latino. Four were homosexual or bisexual male adolescents, and one had hemophilia (San Francisco Department of Public Health, unpublished data, October 1987). Thus, both nationally and locally, reported adolescent AIDS cases and, by inference, HIV infection in adolescents are primarily diseases of older gay male adolescents and those with hemophilia, with a higher proportion of non-whites when compared with AIDS in older persons.

In looking at the potential risk for adolescents, however, it should be noted that the incidence of AIDS rises sharply in the group aged 20 to 24 years, with 1,887 (4.5%) cases

From the Department of Public Health (Drs Oliva, Rutherford, Shalwitz, Taylor, and Werdegar); the Departments of Pediatrics (Drs Oliva, Rutherford, Grossman, and Shalwitz), Family and Community Medicine (Drs Oliva and Werdegar), and Epidemiology and International Health (Dr Rutherford), University of California, San Francisco, School of Medicine; and the National Center for Youth Law (Ms English), San Francisco.

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ABBREVIATIONS USED IN TEXT

AIDS = acquired immunodeficiency syndrome
ARC = AIDS-related complex
CDC = Centers for Disease Control
HIV = human immunodeficiency virus

occurring nationally in this group (Table 1). Because of the long latency period of the disease, it is thought that many of these young adults contracted the infection during adolescence.[7]

HIV Transmission in Households

None of the identified cases of HIV infection in the United States are known to have been transmitted in schools, day care, or foster care settings, or through other casual person-to-person contact.[4] Other than sexual partners of HIV-infected persons, infants born to infected mothers, or two cases involving nonparental transmission of HIV from a patient to a person providing extended home nursing care,[8,9] none of the family members of the more than 40,000 AIDS patients reported to the CDC have contracted AIDS. Eleven studies of family members of patients with HIV infection have failed to show HIV transmission to adults who are not sexual contacts of infected patients or to children who have not already been infected perinatally.[10-20]

Existing Guidelines for Correctional Settings

National recommendations have not been made regarding prevention of HIV infection in correctional settings. In a survey of 50 state correctional departments and 33 large city and county jail systems, none of the eight cases of AIDS in correctional staff were related to inmate contact.[21] Most of the persons with AIDS in prisons and jails were intravenous drug users. Of these institutions, 83% had educational programs for staff and inmates, and most had adopted conservative approaches to testing, with 88% of the state and 79% of the city and county facilities limiting testing to that needed to diagnose symptomatic inmates, testing at the request of inmates, or not doing any testing. Only six state and seven city and county institutions did routine testing. In large part, therefore, correctional institutions have opted for limited testing despite the fact that many deal with large numbers of inmates in well-recognized high-risk groups.

The Legal Rights of Minors

California statutes guarantee minors the right to obtain services for the diagnosis and treatment of sexually transmitted diseases[22] and guarantee without parental consent the provision of services related to pregnancy, pregnancy diagnosis,[23] and chemical dependency.[24] California law also provides minors with the same rights to confidentiality as adults seeking such services[25,26] and requires informed written consent before serologic testing for the presence of HIV may be done or test results disclosed.[27] The current legal interpretation of the above statutes is that adolescents older than 12 years have the same rights to consent and confidentiality in the area of HIV testing as adults have and do not require their parents' consent to be tested. Thus, adolescents should not be tested without their written consent, and their test results should only be disclosed based on their own written authorization. All adolescents should be encouraged to share vital health information with their parents.

Recommendations

Education

Adolescents in school settings. It is imperative that schools provide meaningful information about the modes of transmission and the risks of acquiring HIV infection to students, parents, and teachers. The basic principles of health promotion and communicable disease prevention should be part of the kindergarten through grade 12 curriculum. In addition, instruction in reproductive health, sexual values and attitudes, and the prevention of sexually transmitted diseases including HIV infection should begin in the sixth grade at the latest. All curricula should include information on ways to minimize the risk of acquiring the infection through sexual contact. Personnel responsible for teaching these units should be fully trained and competent in handling the sensitive issues raised by this subject area. Parents should be informed of the inclusion of this material in the curriculum and invited to review and comment on the contents. They should also, where possible, be provided with the opportunity to participate in informational meetings to address their concerns and answer their questions. In addition to previous recommendations regarding education,[3] we recommend that tests of students' knowledge of health issues, including HIV and other communicable diseases, be developed and instituted to guarantee that the material has been taught in an effective manner.

Homeless and truant adolescents. Public and private agencies serving these populations should develop educational materials and intervention strategies that can be integrated into their current programs. Efforts should be made to reach homeless adolescents, including non-English-speaking youth, in areas and population groups not currently served by existing providers. All personnel involved in these programs should be given adequate information and training in the prevention of HIV infection, the identification of those at risk, and the techniques for intervening with adolescents in the area of sexual behavior and intravenous drug use. Sexually active youths should be encouraged to use safe sexual practices, regardless of sexual orientation, drug use, or other risk indicators.

Adolescents in medical settings. This group includes adolescents involved in drug, alcohol, and mental health programs and those receiving family planning services, sexually transmitted disease treatment, and specialized services for

TABLE 1.—*AIDS Cases by Transmission Category and Age Group, United States**

	Cases			
	Age Group, yr			
	13-19		20-24	
Transmission Category	*No.*	*(%)*	*No.*	*(%)*
Homosexual or bisexual man	64	(38)	1,173	(62)
Intravenous (IV) drug user	13	(8)	143	(8)
Homosexual or bisexual man and IV drug user	11	(6)	216	(11)
Hemophilia or coagulation disorder	10	(6)	30	(2)
Transfusion, blood or components	52	(31)	48	(3)
Heterosexual	10	(6)	188	(10)
Undetermined	10	(6)	89	(5)
Total	170		1,887	

AIDS=acquired immunodeficiency syndrome

*Provisional data through October 5, 1987.

homosexuals. We recommend that educational programs similar to those described for homeless and truant adolescents be developed and implemented for this group.

Adolescents in residential settings. Residential settings include foster care, group homes, shelters for homeless adolescents, and residential juvenile justice, mental health, and drug treatment facilities. Because of the special circumstances in these facilities, we recommend a comprehensive approach to HIV prevention education similar to that recommended for schools be adopted. This should include the following:

- Thorough education of staff in the areas of sexuality, sexually transmitted diseases, and HIV prevention, including safe sex guidelines;
- Assurance that staff is competent in providing education in the prevention of AIDS and sexually transmitted diseases;
- Uniform infection control precautions such as those proposed by the CDC[28];
- Development of appropriate materials and group sessions for residents; and
- Education of parents, where possible.

HIV Antibody Counseling and Testing

We think that routine testing for the presence of the HIV antibody is not useful for adolescents and recommend that it not be advocated or required. Antibody testing is appropriate in clinical settings for evaluating adolescent patients with unexplained adenopathy or other signs and symptoms of HIV infection. Testing is also appropriate for adolescent women who are at risk of HIV infection and are contemplating pregnancy. In these instances, testing should be conducted in a medical specialty setting with personnel experienced in the diagnosis and treatment of HIV infection. Anonymous testing at alternate test sites may be appropriate as a health education experience for highly motivated adolescents or for those who have a strong desire to be tested. In any event, testing must be voluntary and, if possible, should not be conducted while an adolescent is in detention. Confidentiality and consent requirements should be strictly observed with respect to any testing of adolescents. Psychological risks to youth known to be depressed or suicidal should be taken into consideration in all pretest and posttest counseling.

Schools. Previously published guidelines developed by the Department of Public Health for the San Francisco Unified School District recommend that widespread school-based educational programs be implemented for students, parents, and teachers.[3] There should be no mandatory HIV antibody testing for school staff or students. There is in general no contraindication for school attendance of HIV-infected children, but decisions regarding placement of students known to be infected with HIV should be reviewed by a joint committee of the Department of Public Health and the school district. Strict confidentiality should be maintained and uniform disinfection procedures adopted.[3]

Pregnant adolescents. Previously published guidelines developed by the Department of Public Health recommended that HIV antibody testing be conducted on a confidential basis with informed consent by the prenatal care provider in the first trimester or as early as possible for women who are at risk of having been exposed to HIV infection.[1]

Residential settings. All adolescents entering a residential setting should have a complete medical evaluation upon admission. Even if the adolescent is found to be at risk for HIV infection, testing should occur only in accordance with the general guidelines stated previously. We do not recommend mandatory testing, regardless of risk status, at this time. There is no reason to require testing of staff.

All residential settings need updated infection control guidelines stressing uniform disinfection procedures for body fluid spills. All staff should be educated about the techniques involved in implementing these guidelines.

Adolescents Known to Be Infected With HIV

We recommend that adolescents known to be infected with HIV have no restrictions placed on access to educational or treatment programs except when their health provider recommends such restrictions to protect them from exposure to infection. Previously published guidelines for the education of children infected with HIV provide for a case review for any infected student enrolling in school.[3] A baseline medical evaluation of any student entering school should be encouraged. Adolescents known to be infected should be aggressively counseled on limiting further transmission of infection and should be offered ongoing psychological counseling in an accessible setting. Additionally, adolescents should be encouraged to inform past, present, and future sexual partners that they may have been exposed.

Youth in detention. All adolescents entering detention should have a thorough medical evaluation. A designated on-site physician should determine whether adolescents can be housed in a routine setting or whether there needs to be a more protected environment. Routine isolation is not indicated. Regardless of the placement decision, the right of an adolescent to confidentiality must be maintained. The fact that an adolescent is infected should not be disclosed to anyone, including other detained adolescents, probationary counselors, or residential staff, except for medical staff involved in the adolescent's direct care. Protocols should be developed to guarantee confidentiality of medical records. Staff should follow uniform infection control procedures in these settings, whether or not the facility is housing HIV-infected persons.

Youth in other residential facilities. There is in general no reason to exclude HIV-infected adolescents from a residential setting. Medical review should be done before placement, however, to determine any special needs. Confidentiality should be carefully maintained. HIV status should not be disclosed to social service, legal, or probation personnel unless, as determined in the medical review, such disclosure is necessary for the protection of the adolescent or others with whom he or she may have contact. Disclosure to anyone other than the health care provider should occur only with the written consent of the adolescent or on court order when deemed medically necessary. Adolescents who are clinically ill will require special care, and this should be arranged on a case-by-case basis.

Special confidential counseling should be available for infected adolescents in all residential settings. Circumstances may dictate whether it is wise to provide this on or off site. This counseling should include psychosocial support and coordination of services that the adolescent currently needs or will need to cope with the disease. Detailed infor-

mation on the modes and prevention of transmission should be provided.

Asymptomatic Adolescents With High-Risk Behaviors Whose Antibody Status Is Unknown

Intensive educational efforts should be targeted to asymptomatic adolescents who are known to engage in high-risk behavior but whose antibody status is unknown, as well as to their service providers. As long as the incidence of HIV infection and clinical AIDS remains low in adolescents, there should be no restrictions on residential placements and no routine testing done, including testing of those housed in correctional settings. Adolescents who have been counseled and request testing should be referred to anonymous test sites.

Conclusions

These are interim guidelines that will be regularly reviewed as more information becomes available on the incidence and natural history of HIV infection in adolescents. We emphasize that the prevalence of HIV infection among adolescents appears to be low and that there is no evidence that HIV is transmitted among adolescents not involved in sexual contact with infected partners, not sharing needles, and not exposed to blood or blood products. We conclude that routine testing for HIV infection should not be conducted in any group of adolescents at this time.

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Progress in Medical Science

Fetal Endoxins and Complications of Pregnancy

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Maternal endoxin (digoxinlike substance) is proposed as arising in the fetal area of the fetal adrenal cortex. Its function may be to sensitize the uterus for labor, much as does cortisol in the sheep fetus. Because endoxin is a sodium-potassium-adenosine triphosphatase inhibitor, however, it may also induce maternal vasoconstriction. On our service, normal pregnant women have detectable endoxin after 35 weeks with increasing amounts at term. Specimens of cord blood often have "digoxin" in the therapeutic range. We find that about 40% of women in premature labor and 65% of pregnant women with hypertension have elevated levels of serum endoxin. Postdate gravid women sometimes have very low endoxin levels. Pregnant women with complications and elevated digoxin (endoxin) levels could have specific antidigoxin therapy if endoxin proves to be a modulator of their symptoms. Digoxinlike substances are also sometimes elevated in ill nonpregnant persons, such as those with renal, liver, or heart failure, or hypertension.

(Goodlin RC, Makowski EL: Fetal endoxins and complications of pregnancy. West J Med 1988 May; 148:590-592)

In 1961 de Wardener and associates began a provocative series of studies that suggested that intravascular volume expansion caused natriuresis and that this effect was mediated in part by a humoral substance.[1] Evidence was also presented in 1969 for an endogenous inhibitor of the sodium-potassium-adenosine triphosphatase (ATPase) enzyme that was natriuretic and inhibited sodium transport of isolated amphibian membranes.[2] Decreased sodium transport across frog skin in the presence of serum from patients with preeclampsia was reported in 1972 and 1979.[3] Kuhnert and colleagues found that newborns of preeclamptic mothers had significantly less erythrocytic Na-K-ATPase activity. They suggested that this disruption of fetal sodium transport was consistent with a circulating "toxin."[4]

Background

Gruber and co-workers coined the term "endoxin" for the putative natriuretic hormone that also reacts with digoxin antibodies.[5] (Endoxin is not related to atrial natriuretic factor.) Other terms used include digoxinlike substance (DLS), digoxinlike immunoreactive substance, cardiodigin, endocardin, endalin, and ouabainlike substance.[6] Based on renal perfusion studies, Ahmad and colleagues showed in dogs that DLS is a marker for a natriuretic hormone.[7] Endoxin (digoxin) is considered to be present in human fluids and tissues that inhibit Na-K-ATPase and displace labeled ouabain from Na-K-ATPase.[8] Endoxin or DLS levels are also increased in the serum and urine of some adults with liver or renal failure, and endoxin is present in high concentrations in the umbilical cord blood of normal humans and higher primates.[9] The fetoplacental unit is the probable source of maternal endoxin in late normal pregnancy because maternal serum values decrease to undetectable levels immediately after delivery.[9] Two patients on our service with severe postpartum toxemia and liver involvement had elevated endoxin levels. Pregnant women, apparently like other adults with liver or renal failure, may produce their own endoxin. In humans, newborn urine and serum endoxin levels usually disappear one to three weeks after birth, but measurable levels may sometimes remain for months. It is postulated that endoxin might be among the pathologic factors involved in hyponatremia in premature infants.[10,11] Based on the results of catheterization, organ extracts, and radioimmunoassay staining studies, the adrenal glands are considered one of the sites of endoxin production.[12] Endoxin from the adrenal gland is probably a steroid, but if it is produced in the hypothalamus, it may be a peptide.[9] Recent studies suggest that endoxin exists in serum in three forms—protein-bound, glucuronidated, and free—and, in urine, as glucuronidated and free.[13]

Wijdicks and associates found DLS in patients with hypothalamic damage from subarachnoid hemorrhage who were in negative sodium balance, suggesting that either the hypothalamus produces DLS or it stimulates the adrenal cortex to synthesize DLS.[14] Toxemic pregnant women with hyponatremia may also have significantly elevated levels of endoxin.[15] While some have suggested that DLS represents at least 40 different substances,[16] the digoxin antibody is highly specific. Furthermore, essentially the same endogenous digoxins are suggested when an enzymatic or ouabain receptor test, rather than an immunoreactive assay, is used for measuring digoxin levels.[17,18]

Because endoxin has been proposed as an inhibitor of sodium, potassium, and calcium exchange—a Na-K-ATPase inhibitor—it is also likely to be a peripheral vasoconstrictor and hypertensive agent. Endoxin inhibition of the sodium pump at the level of the vascular smooth muscle cells leads to increased intracellular calcium, which is presumed to mediate a rise in the basal tone that enhances the response to vasoconstrictor agents.[19] Norris likewise showed that on an isolated human uterine muscle strip, digoxin produced increased tone and contractions.[20] Nifedipine, a potent Ca^{++}

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ABBREVIATIONS USED IN TEXT

ATPase = adenosine triphosphatase
DLS = digoxinlike substance

entry blocker and a hypotensive and tocolytic agent clinically, abolishes or antagonizes digoxin and ouabain-induced peripheral vasoconstriction.[21,22] While digoxin causes a rise in tension of human placental arteries, this effect is not abolished by nifedipine.[23]

During a normal pregnancy there is a progressive rise of serum endoxin and the increment, in part depending on the digoxin assay kit or batch used.[6] In our clinical laboratory studies, no normal pregnant woman has had detectable digoxin in her serum (more than 0.2 ng per ml) before 35 weeks.[24] In 1984 both Beyers and colleagues in South Africa and Gudson in North Carolina reported finding elevated levels of digoxinlike substance in the serum of pregnant women with preeclampsia and in their newborns, with umbilical cord values being the highest when compared with those of newborns from normal pregnancies.[25,26] Repeat studies in 1986 by Odendaal and co-workers failed to confirm that maternal serum preeclamptic values were higher but again noted that serum levels from newborns were significantly increased above those from newborns of normal pregnancies.[27] Other studies have shown that sodium concentrations in erythrocytes are substantially increased in hypertensive pregnant women. Such findings are consistent with the inhibition of Na-K-ATPase.[6,9] While Gonzalez and colleagues found increasing DLS levels with advancing normal pregnancy, however, their preeclamptic patients had lower serum digoxin levels than did normal pregnant women.[28]

No investigator has apparently correlated maternal values of digoxin with renal function. This probably explains why only some patients with preeclampsia have highly increased values. Our own studies showed that no preeclamptic patient with a blood urea nitrogen level below 10 mg per dl had elevated serum digoxin values but that their urinary values of DLS are elevated.

It may be through the fetal adrenal cortex, with increased excretion of endoxin, that the human fetus is responding to stress and is exerting a role in what it senses to be the timely onset of labor, much as has been described in sheep fetuses.[29] An untoward effect of abnormal fetal endoxin activity could be to sensitize the mother's vascular system and uterus, leading to vasoconstriction, premature labor, or both. Presumably, fetal adrenal steroid, related in other species (such as cortisol in sheep) to preparation for labor, does not have these postulated maternal vasoconstrictor properties. High fetal endoxin levels as a fetal adrenal response to stress could also partially explain the recognized variable placental transfer and fetal cardiac response to maternal digoxin administration by blocking fetal digoxin receptors.[30] That endoxin is at least a modulator of labor is supported by our observation that 30% of postdate pregnant women have considerably reduced maternal digoxin levels.

Contrary to our hypothesis, however, we have noted that some pregnant women may have high levels of endoxin, such as when their fetus has the adrenogenital syndrome, without either the onset of labor or maternal hypertension. Gruber and associates likewise observed that asymptomatic dogs may have high levels of endoxin.[5] In support of the fetal adrenal origin theory, we have not found endoxin (more than 0.2 ng per ml) in maternal or cord blood of two patients with anencephalic newborns. Furthermore, maternal levels decrease after dexamethasone therapy.[24]

Rationale for Antidigoxin Therapy

In deoxycorticosterone acetate-salt hypertensive rats with elevated levels of DLS or endoxin, the administration of an immunoglobulin G antidigoxin serum (anti-DLS) causes a pronounced decrease in hypertension.[31] Serum endoxin (digoxin) levels have been noted to be especially elevated in 21 pregnant women with the HELLP syndrome (hemolysis, elevated liver enzymes, low platelets) and in 45 preeclamptic patients with predominantly renal or liver involvement.[32] Of pregnant women delivering before 35 weeks on our service, 40% had serum values of endoxin greater than or equal to those delivering at term. Most of these women were delivered of infants who were growth-retarded or small for gestational age, but others had only premature labor.[24]

An antidigoxin Fab fragment, Digibind, has been approved for marketing in the United States for intravenous treatment of potentially life-threatening digoxin toxicity. No adverse reactions have been reported with Digibind in the treatment of digoxin toxicity except a possible exacerbation of the initial cardiac condition.[33] In humans the transplacental transfer of antibodies is dependent on Fc receptors at the syncytiotrophoblast membrane. These human placental Fc receptors become active only after 31 weeks' gestation, suggesting that the Fab antidigoxin would not be transferred to fetuses of less than 31 weeks' gestation.[34] There is no reason to think, therefore, that the use of Digibind would be detrimental to a fetus if used in women with nonviable pregnancies (less than 26 weeks) with life-threatening toxemia. Fetuses delivered before 26 weeks of gestation have less than a 10% chance of survival. After her treatment had been approved by our human subject committee, a pregnant woman at 25½ weeks' gestation with severe hypertension and increased digoxin levels had, as in animal studies, a notable hypotensive response to 10 mg of Digibind administered intravenously.

Nifedipine has been used successfully for both the treatment of hypertension and of premature labor[35,36] without regard to maternal digoxin levels. Given its antagonistic digoxin activity, it would, according to our theory, be more effective in pregnant women with these complications who also have substantially elevated digoxin levels. Likewise, if asymptomatic high-risk pregnant women had a positive urine or serum screening test for elevated levels of digoxin, low-dose nifedipine may prove to be an effective prophylactic drug.

A third possible therapy is the use of spironolactone for patients with elevated endoxin levels. Spironolactone and its metabolite canrenone are known to be partial agonists at the sodium pump receptor site; their use in humans is supported by the association with increased serum levels of digoxinlike substance.[9,37] The use of spironolactone in pregnant women has been limited because of its major effects on serum electrolyte levels, but it may have less deleterious effects than those antidigoxin drugs previously discussed.

Endoxin Screening in Pregnant Women

Screening of pregnant women for endoxin could be enhanced by only using an antidigoxin antibody that reacts with

pooled human umbilical cord blood because this is the postulated source of increased maternal endoxin. Comparison with such a standard would avoid the variability now found in various commercial preparations.[38] A urine endoxin screen is possible[6,9] and would be the most acceptable for monitoring pregnant patients at risk, in terms of both convenience and circumventing problems of variable renal function.

Endoxin Studies in Nonpregnant Persons

In addition to the previously cited reviews of Valdez[6] and Graves,[9] other studies of elevated "digitalis-like" compounds reported three times higher serum levels in hypertensive men than in normal controls.[39] Other recent reviews have concluded that most likely the Na-K-ATPase inhibitor was not a peptide[40] and that there may be more than one such agent. Haddy also concluded that endogenous "digitalis" is relevant to adult volume control and low-renin hypertension. It is considered possible that the hypothalamus may influence and control the secretion of endoxin from another source, such as the adrenal gland, and that the agent may be a steroid similar to the cardiac glycosides.[41]

Addendum

According to its manufacturer, the TDx II digoxin antibody used in this study has been changed to minimize or eliminate DLS "interference" (E. S. Jenest, Abbott Laboratories, written communication, January 1988).

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A Survey on the Prevalence of Alcoholism Among the Faculty and House Staff of an Academic Teaching Hospital

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We studied the extent of alcoholism among faculty and house staff of an urban, university-based teaching hospital. Of 569 questionnaires sent, 282 (50%) were returned and 271 of these were complete enough to be interpretable. Of those responding, 12 (4%) were classified as alcoholic and 26 (10%) as possibly alcoholic. There was no statistically significant difference in the prevalence of alcoholism in physicians from the different medical specialties or in regard to gender. Nevertheless, with 14% of the respondents to our questionnaire being classified as either alcoholics or possible alcoholics, it appears that this is a pervasive problem in our profession that deserves further study.

(Siegel BJ, Fitzgerald FT: A survey on the prevalence of alcoholism among the faculty and house staff of an academic teaching hospital. West J Med 1988 May; 148:593-595)

In the last decade a great deal has been written about the problem of alcoholism among physicians. Very little is known about the actual prevalence of this problem, however. A 1986 review of the literature on alcoholism and drug abuse among physicians suggests that the true prevalence of alcoholism in this group is unknown.[1] To date there have been only two published reports of surveys of physicians where standard measures of alcoholism were used. Both of these surveys, however, were administered only to subgroups of physicians that were not necessarily representative of physicians as a whole, and the prevalence of alcoholism reported in these studies differed markedly.[2,3] Accurately assessing the magnitude of alcoholism in medical professionals, especially physicians, is clearly a matter of considerable importance. The definition, identification, and treatment of impaired physicians is of immediate concern to patients, regulatory boards, and society as a whole. To obtain more information on the prevalence of alcoholism among physicians, we surveyed a broad group of physicians.

Materials and Methods

A slightly modified version of the Short Michigan Alcoholism Screening Test was sent to all faculty and house staff of an urban, university-based teaching hospital (Figure 1). The only notable modification of the questionnaire was the addition of a second component to question six, where respondents were asked whether their attendance at a meeting of Alcoholics Anonymous was part of a class assignment or a clinical rotation. Limited demographic information was also requested. Each alcoholism-indicating response was assigned a one-point value. Respondents scoring zero to one point were classified as nonalcoholic. Those with two points were considered to be possibly alcoholic. Those scoring three or more points were classified as alcoholic. This system is similar to that used by Selzer and colleagues.[4] The data were analyzed using the Catmod procedure in the statistical analysis system and a mainframe computer.[5]

Results

House staff and faculty were sent 569 questionnaires. Of these, 282 (50%) were returned, with 271 complete enough to be interpretable and scored in the manner described in the methods section. These constituted the final sample upon which we based our results. A total of 12 (4%) of the respondents scored 3 or more points and were classified as alcoholic. An additional 26 (10%) respondents scored 2 points and were classified as possibly alcoholic. The remaining 233 respondents scored 1 or fewer points and were classified as nonalcoholic.

Of the 271 respondents, 147 (54%) identified themselves as men. Of these, 6 (4%) were alcoholic and 16 (11%) were possibly alcoholic. A total of 43 (16%) of the respondents identified themselves as women; one (2%) was classified as alcoholic and three (7%) were classified as possibly alcoholic. Of the 81 subjects who declined to state their sex, there were 5 (6%) alcoholics and 7 (9%) possible alcoholics (Table 1). There was no statistically significant difference in the prevalence of alcoholism among these three groups (χ^2 with 4 degrees of freedom $(df) = 1.8, P = .77$).

We also examined the influence of the respondents' medical specialty on the prevalence of alcoholism. The only specialties in which no one was identified as being either alcoholic or possibly alcoholic were physical medicine and rehabilitation and therapeutic radiology. The highest prevalence of alcoholism was found in the specialties of family practice and obstetrics and gynecology, where 14% of the respondents were identified as being alcoholic. No one identifying themselves as a member of the specialties of anesthesiology, physical medicine and rehabilitation, therapeutic radiology, or psychiatry was classified as an alcoholic. The highest prevalence of those classified as possibly alcoholic was found in the group containing pathology, radiology, and nuclear medicine, in which 36% of the respondents fell. Among those respondents who declined to state their spe-

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TABLE 1.—*Effects of Gender on Prevalence of Alcoholism*

Gender	Non-alcoholic, No. (%)	Possibly Alcoholic, No. (%)	Alcoholic, No. (%)	Total, No. (%)
Men	125 (85)	16 (11)	6 (4)	147 (54)
Women	39 (91)	3 (7)	1 (2)	43 (16)
Decline to state	69 (85)	7 (9)	5 (6)	81 (30)
Total	233 (86)	26 (10)	12 (4)	271

cialty, only 5% were classified as alcoholic and the rest were classified as nonalcoholic (Figure 2). Despite the extreme variation in the prevalence of alcoholism among various departments, the null hypothesis that the mean of all of the departments is equal cannot be rejected (χ^2 with 18 df = 27.3, P = .07).

Discussion

Previous estimates of the prevalence of alcoholism among physicians have varied widely. Murray suggested that it is much higher than that in the general population,[6] while other investigators have suggested with equal conviction that it is probably no greater than that of the general population.[7,8] Our knowledge of the true extent of the problem is hampered by the application of an often imprecise definition of alcoholism, the surveillance of only highly selected subpopulations, such as hospitalized patients or those physicians in trouble with medical disciplinary or licensing boards, and, perhaps, the failure of physicians to make this diagnosis in their peers.[1,9]

Thus far, there have been only two reports in the literature wherein alcoholism-indicating surveys have been used to determine the prevalence of alcoholism in physicians. The first study was conducted on a group of physicians, most of whom were family practitioners, attending a continuing medical education conference. The Self-Administered Alcoholism Screening Test was completed by 399 physicians. By this instrument, the authors concluded that this group had 2% alcoholics and 5% possible alcoholics.[2] These results are quite different from those published in the only other study in which an alcoholism-indicating survey was used. In this study, the Michigan Alcoholism Screening Test was sent to all of the house staff of the Presbyterian Hospital in New York. Of the 417 house staff surveyed, 188 responded. Of these, 13% had scores that indicated either suggested or presumed alcoholism.[3]

Based on these studies, the prevalence of dysfunctional drinking in physicians would appear to be anywhere from 7% to 13%. There are many possible explanations for this disparity. In the Lewy survey, questionnaires were mailed, and the participants may have felt that their anonymity was more secure than that of physicians at a continuing education conference. Thus, they may have answered their questionnaires with greater candor, resulting in a higher number of identified alcoholics. Alternatively, the participants in the survey of house staff may have been much younger than those who attended the continuing education conference. If young physicians drink more heavily than older ones, this could also account for the difference in the prevalence of dysfunctional drinking in these two studies. Also, those who attend continuing educational conferences are a self-selected group. Perhaps the conference where the survey took place in the study by Niven and associates was such that it selected for nonalcoholic physicians, and the prevalence of alcoholism, therefore, was found to be lower than that in a random group of house staff.

To obtain more precise information on the prevalence of alcoholism in physicians, we decided to apply a structured, validated, alcoholism-indicating questionnaire to a broad-based group of working physicians in multiple disciplines over a wide age range.

In our study of the house staff and faculty of a university-based teaching hospital, 4% of the respondents were identified as being alcoholic and 10% as being possible alcoholics. These findings stand in marked contrast to the prevalence of alcoholism reported in the study of physicians attending a continuing education conference. The prevalence of dysfunctional drinking in our group is also higher than that reported in the house staff at Presbyterian Hospital.

1. Do you feel you are a normal drinker? (By normal, we mean you drink less than or as much as most people.)
2. Does your **spouse,** a parent, or other near relative ever worry or complain about your drinking?
3. Do you ever feel guilty about your drinking?
4. Do friends or relatives think you are a normal drinker?
5. Are you able to stop drinking when you want to?
6. Have you ever attended a meeting of Alcoholics Anonymous? **If you answered yes, was this part of a class assignment or clinical rotation?**
7. Has drinking ever created problems between you and your **spouse,** a parent, or other near relative?
8. Have you ever gotten into trouble at work because of drinking?
9. Have you ever neglected your obligations, your family, or your work for two or more days in a row because you were drinking?
10. Have you ever gone to anyone for help about your drinking?
11. Have you ever been in a hospital because of drinking?
12. Have you ever been arrested for drunken driving, driving while intoxicated, or driving under the influence of alcoholic beverages?
13. Have you ever been arrested, even for a few hours, because of other drunken behavior?

Figure 1.—Modified Short Michigan Alcoholism Screening Test, with modifications placed in bold-faced type.

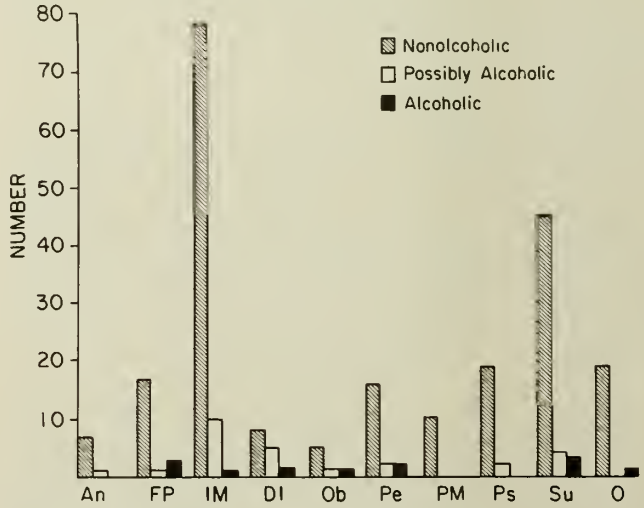

Figure 2.—The graphs show the number of respondents by medical specialty. An = anesthesiology; FP = family practice; IM = internal medicine and related specialties; DI = pathology, radiology, and nuclear medicine; Ob = obstetrics and gynecology; Pe = pediatrics; PM = physical medicine and rehabilitation and therapeutic radiology; Ps = psychiatry; Su = surgery and its subspecialties; O = declines to state

There was no statistically significant difference in our cohort in the incidence of alcoholism by sex of the respondent, but almost 30% of our respondents declined to identify their gender, perhaps out of fear of being identified. Thus, we can say little from our data about the true relationship between gender and alcoholism in physicians.

Medical specialty also bore no statistically significant relationship to alcoholism in our study. However, a pronounced variation was noted in the prevalence of alcoholism in different specialties and may have achieved statistical significance had the cohort been larger. It was striking to note the high number of alcoholics in the specialties of family practice and obstetrics and gynecology compared to none in anesthesiology, physical medicine and rehabilitation, therapeutic radiology, or psychiatry.

Since slightly more than half of those surveyed did not return their questionnaires, it would be hazardous to draw any firm conclusions from this study—we have no knowledge of the prevalence of alcoholism among those who did not return the questionnaire. Yet, with 14% of those who did respond being classified as either alcoholics or possible alcoholics, it appears that this may be a pervasive problem that clearly demands further study.

If further studies do substantiate this high rate of alcoholism, what can be done about it? How can physicians, hospitals, and state licensing boards concurrently assure the best therapy for those physicians affected, as well as protection for them and for their patients? Rehabilitation can be more successful in alcoholic physicians than in nonphysician alcoholics. In one report, 76% of alcoholic physicians were abstaining one year after discharge from treatment, as opposed to 61% of patients in the general population.[10] National, state, and hospital boards have constructed detection and therapy programs for impaired physicians that have been effective.[11-13] Reluctance to identify and "stigmatize" professional colleagues with a diagnosis of alcoholism is a major impediment to care.[9] We must continue to design programs aimed at educating physicians and medical students in the realities of alcoholism and its treatment, the prevalence of this disease, and the availability of Alcoholics Anonymous and other rehabilitation programs.

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Lessons From the Practice

A Special Birth, a Special Baby

JOSEPH E. SCHERGER, MD, *Davis, California*

When Gail and Doug came for prenatal care, I was happy to see them again. I had delivered their third child two years earlier, and they chose to come from a neighboring town in order for me to deliver their new baby.

Gail's prenatal course was painful, though obstetrically satisfactory. Her weakened lumbosacral spine gave out during the second trimester. The severe pain reduced her to moving about the house on her hands and knees to care for her three children. She rejected my chairs and examination table and would be lying on the floor when I entered the room. With enforced but reluctant bedrest, physical therapy, and transcutaneous nerve stimulation, her back pain lessened during the last month of pregnancy.

With their strong Christian faith and abhorrence for abortion under any circumstances, Gail and Doug rejected α fetoprotein screening. At age 34, Gail was not a candidate for routine amniocentesis, but she would have refused this also. Fetal growth was steady but lagged behind the norm and her previous pregnancies. Our concern about the size of the fetus was defused by Gail's faith that the baby was fine.

Labor started 20 days before Gail's due date, with an estimated fetal weight of 6½ pounds. Gail was in good control—conversant and good humored between contractions. Doug was a great partner, coach, and back massager. Gail labored mostly on her side, and the pain from her back and the labor was not severe. Fetal heart tones were good, and the labor progressed normally.

We will all remember the birth forever. Adopting the attitude and approaches of Michel Odent (*Birth Reborn,* New York, Pantheon Press, 1984), I kept my hands off Gail and the baby as much as possible. Standing back from the foot of the bed, I saw her eyes gleam intensely as she exclaimed, "The baby is coming!" She reached down to cradle the head as it eased from her vagina. With encouragement, she then delivered her own baby by pushing out the shoulders, grasping the trunk under the arms, and bringing her little girl to her chest.

I immediately saw the problem—a blue-gray opening covered by a thin membrane at the base of the baby's spine. The baby had a myelomeningocele. I explained the situation to Gail and Doug and took the baby to the nursery for protection of the defect and resuscitation. The baby required oxygen and positive pressure application for a few minutes to obtain a good heart rate, respiration, and color. I called for a transport team from the university medical center.

The full extent of baby Naomi's problems became evident after a week at the medical center. She had trisomy 9 mosaicism, myelomeningocele repaired, tetralogy of Fallot, coloboma with associated eye abnormalities, bilateral hip dislocation, and poor feeding. Naomi would likely be severely retarded, and her prognosis for life beyond a few months was poor. Despite all of this, Gail, Doug, and I could not help but feel how cute and precious she was.

A week after Naomi's birth, while the extent of her problems was being unraveled, Gail tearfully expressed appreciation to me for the beautiful birth. Being able to deliver her own baby to her chest was a joy that all that followed could not lessen.

Gail and Doug brought Naomi to the office for biweekly visits, and she stayed remarkably the same. Her weight remained at 6½ pounds. Her suck improved, and she even nursed a little. Her sounds were sweet and unique. She looked and felt like a live little doll. She was good. Being with her gave us no sense of tragedy.

Naomi died at home after seven weeks of life. About 24 hours before her death she started having apneic spells that became more frequent and prolonged. Physicians in the medical center emergency room found no signs of infection or heart failure; the apnea was most likely due to neurologic deterioration. Naomi returned home to spend her last hours with her parents and with her three brothers and sisters. I sat in the home with Gail and Doug, and we talked about how special Naomi was.

As a family physician delivering babies for the past ten years, I had dreaded the first time I would deliver a baby with major birth defects. Birth is the gift of life and everyone wants a healthy baby. I work hard to make birth a positive experience, and I imagined being set up for a major disappointment with a "bad outcome." Gail, Doug, and Naomi taught me that having a child with birth defects can also be a positive experience.

* * *

"Lessons From the Practice" presents a personal experience of practicing physicians, residents, and medical students that made a lasting impression on the author. These pieces will speak to the art of medicine and to the primary goals of medical practice—to heal and to care for others. Physicians interested in contributing to the series are encouraged to submit their "lessons" to the series' editors.

JONATHAN E. RODNICK, MD
STEPHEN J. McPHEE, MD
Series' Editors

(Scherger JE: A special birth, a special baby. West J Med 1988 May; 148:596)

From the Department of Family Practice, University of California, Davis, School of Medicine.
Reprint requests to Joseph E. Scherger, MD, Department of Family Practice, TB 152, University of California, Davis, School of Medicine, Davis, CA 95616.

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Programmed delivery *in vivo* of 0.1, 0.2 or 0.3 mg clonidine per day, for one week.

Brief Summary of Prescribing Information

Contraindications: Catapres-TTS® (clonidine) should not be used in patients with known hypersensitivity to clonidine or to any other component of the adhesive layer of the therapeutic system.

Precautions: ***General:*** In patients who have developed localized contact sensitization to Catapres-TTS® (clonidine), substitution of oral clonidine hydrochloride therapy may be associated with development of a generalized skin rash.

In patients who develop an allergic reaction to Catapres-TTS® that extends beyond the local patch site (such as generalized skin rash, urticaria, or angioedema) oral clonidine hydrochloride substitution may elicit a similar reaction.

As with all antihypertensive therapy, Catapres-TTS® should be used with caution in patients with severe coronary insufficiency, recent myocardial infarction, cerebrovascular disease, or chronic renal failure.

Transdermal clonidine systems should be removed before attempting defibrillation or cardioversion because of the potential for altered electrical conductivity that may enhance the possibility of arcing, a phenomenon associated with the use of defibrillators.

Withdrawal: Patients should be instructed not to discontinue therapy without consulting their physician. Sudden cessation of clonidine treatment has resulted in subjective symptoms such as nervousness, agitation and headache, accompanied or followed by a rapid rise in blood pressure and elevated catecholamine concentrations in the plasma, but such occurrences have usually been associated with previous administration of high oral doses (exceeding 1.2 mg/day) and/or with continuation of concomitant beta-blocker therapy. Rare instances of hypertensive encephalopathy and death have been reported.

An excessive rise in blood pressure following Catapres-TTS® discontinuance can be reversed by administration of oral clonidine or by intravenous phentolamine. If therapy is to be discontinued in patients receiving beta-blockers and clonidine concurrently, beta-blockers should be discontinued several days before cessation of Catapres-TTS® administration.

Perioperative Use: As with oral clonidine therapy, Catapres-TTS® therapy should not be interrupted during the surgical period. Blood pressure should be carefully monitored during surgery and additional measures to control blood pressure should be available if required. Physicians considering starting Catapres-TTS® therapy during the perioperative period must be aware that therapeutic plasma clonidine levels are not achieved until 2 to 3 days after initial application of Catapres-TTS®.

Information for Patients: Patients who engage in potentially hazardous activities, such as operating machinery or driving, should be advised of a potential sedative effect of clonidine. Patients should be cautioned against interruption of Catapres-TTS® therapy without a physician's advice. Patients should be advised that if the system begins to loosen from the skin after application, the adhesive overlay should be applied directly over the system to ensure good adhesion over its 7-day lifetime. Instructions for using the system are provided. Patients who develop moderate or severe erythema and/or localized vesicle formation at the site of application, or a generalized skin rash, should consult their physician promptly about the possible need to remove the patch.

Drug Interactions: If a patient receiving clonidine is also taking tricyclic antidepressants, the effect of clonidine may be reduced, thus necessitating an increase in dosage. Clonidine may enhance the CNS-depressive effects of alcohol, barbiturates or other sedatives. Amitriptyline in combination with clonidine enhances the manifestation of corneal lesions in rats.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In a 132-week (fixed concentration) dietary administration study in rats, clonidine hydrochloride administered at 111 to 160 times the maximum recommended daily human dose (MRDHD) of Catapres-TTS® (clonidine) was unassociated with evidence of carcinogenic potential. Results from the Ames test with clonidine hydrochloride revealed no evidence of mutagenesis. Fertility of male or female rats was unaffected by doses of clonidine hydrochloride as high as 150 mcg/kg or about 10.5 times the MRDHD of Catapres-TTS® (clonidine). Fertility of female rats did, however, appear to be affected (in another experiment) by doses of clonidine hydrochloride at 500 to 2000 mcg/kg or 35 to 140 times the MRDHD of Catapres-TTS® (clonidine).

Pregnancy: Teratogenic Effects. Pregnancy Category C. Reproduction studies performed in rabbits at doses up to approximately 10.5 times the maximum recommended daily human dose (MRDHD) of Catapres-TTS® (clonidine) have revealed no evidence of teratogenic or embryotoxic potential in rabbits. In rats, however, doses as low as 1.2 times the MRDHD of clonidine were associated with increased resorptions in a study in which dams were treated continuously from 2 months prior to mating. Increased resorptions were not associated with treatment at the same or at higher dose levels (up to 10.5 times the MRDHD of clonidine) when dams were treated days 6-15 of gestation. Increased resorptions were observed at much higher levels (140 times the MRDHD of clonidine) in rats and mice treated days 1-14 of gestation (lowest dose employed in that study was 500 mcg/kg). There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers: As clonidine is excreted in human milk, caution should be exercised when Catapres-TTS® (clonidine) is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in children below the age of 12 have not been established.

Adverse Reactions: Most systemic adverse effects during therapy with Catapres-TTS® (clonidine) have been mild and have tended to diminish with continued therapy. In a 3-month, multiclinic trial of Catapres-TTS® in 101 hypertensive patients, the most frequent systemic reactions were dry mouth (25 patients) and drowsiness (12 patients).

Transient localized skin reactions, primarily localized pruritus, occurred in 51 patients. Twenty-six patients experienced localized erythema. This erythema and pruritus were more common in patients utilizing an adhesive overlay for the entire 7-day treatment period. Allergic contact sensitization to Catapres-TTS® was observed in 5 patients.

In additional clinical experience contact dermatitis resulting in treatment discontinuation was observed in 128 of 673 patients (about 19 in 100) after a mean duration of treatment of 37 weeks. The incidence in white females was about 34 in 100; in white males about 18 in 100; in black females about 14 in 100; and in black males about 8 in 100.

The following less frequent adverse experiences were also reported in patients involved in this multiclinic trial with Catapres-TTS®:

Gastrointestinal: Constipation (1 patient); nausea (1); and change in taste (1).

Central Nervous System: Fatigue (6 patients); headache (5); lethargy (3), sedation (3); insomnia (2); dizziness (2); and nervousness (1).

Genitourinary: Impotence/sexual dysfunction (2 patients).

Dermatological: Localized vesiculation (7 patients); hyperpigmentation (5), edema (3); excoriation (3), burning (3); papules (1), throbbing (1); blanching (1), and generalized macular rash (1).

In additional clinical experience involving 3539 patients, less common dermatologic reactions have occurred, where a causal relationship to Catapres-TTS® was not established, maculopapular skin rash (10 cases); urticaria (2 cases); angioedema involving the face (2 cases), one of which also involved the tongue.

Oro-otolaryngeal: Dry throat (2 patients).

In long experience with oral Catapres,® the most common adverse reactions have been dry mouth (about 40%), drowsiness (about 35%) and sedation (about 8%). In addition, the following adverse reactions have been reported less frequently.

Gastrointestinal: Nausea and vomiting, about 5 in 100 patients, anorexia and malaise, each about 1 in 100, mild transient abnormalities in liver function tests, about 1 in 100; parotitis, rarely.

Metabolic: Weight gain, about 1 in 100 patients, gynecomastia, about 1 in 1000; transient elevation of blood glucose or serum creatine phosphokinase, rarely.

Central Nervous System: Nervousness and agitation, about 3 in 100 patients; mental depression, about 1 in 100 and insomnia, about 5 in 1000. Vivid dreams or nightmares, other behavioral changes, restlessness, anxiety, visual and auditory hallucinations and delirium have been reported.

Cardiovascular: Orthostatic symptoms, about 3 in 100 patients; palpitations and tachycardia, and bradycardia, each about 5 in 1000. Raynaud's phenomenon, congestive heart failure, and electrocardiographic abnormalities (i.e. conduction disturbances and arrhythmias) have been reported rarely. Rare cases of sinus bradycardia and atrioventricular block have been reported, both with and without the use of concomitant digitalis.

Dermatological: Rash, about 1 in 100 patients; pruritus, about 7 in 1000; hives, angioneurotic edema and urticaria, about 5 in 1000; alopecia, about 2 in 1000.

Genitourinary: Decreased sexual activity, impotence and loss of libido, about 3 in 100 patients; nocturia, about 1 in 100, difficulty in micturition, about 2 in 1000; urinary retention, about 1 in 1000.

Other: Weakness, about 10 in 100 patients; fatigue, about 4 in 100, headache, and discontinuation syndrome, each about 1 in 100; muscle or joint pain, about 6 in 1000 and cramps of the lower limbs, about 3 in 1000. Dryness, burning of the eyes, dryness of the nasal mucosa, pallor, weakly positive Coombs' test, increased sensitivity to alcohol and fever have been reported.

How Supplied: Catapres-TTS®-1 (clonidine) and Catapres-TTS®-2 are supplied as 4 pouched systems and 4 adhesive overlays per carton, 3 cartons per shipper (NDC 0597-0031-12 and 0597-0032-12, respectively.) Catapres-TTS®-3 is supplied as 4 pouched systems and 4 adhesive overlays per carton (NDC 0597-0033-34).

	Programmed Delivery Clonidine *in vivo* per Day Over 1 Week	Clonidine Content	Size	Code
Catapres-TTS®-1	0.1 mg	2.5 mg	3.5 cm2	BI-31
Catapres-TTS®-2	0.2 mg	5.0 mg	7.0 cm2	BI-32
Catapres-TTS®-3	0.3 mg	7.5 mg	10.5 cm2	BI-33

Boehringer Ingelheim

Boehringer Ingelheim Pharmaceuticals, Inc. Ridgefield, CT 06877

Consult package insert before prescribing.

CT-BPI-10/86

In Memoriam

(Continued from Page 534)

TAYLOR, ROBERT G., Sacramento. Died Jan 3, 1988, aged 62. Graduate of University of Tennessee College of Medicine, Memphis, 1952. Dr Taylor was a member of the Sacramento-El Dorado Medical Society.

THORNER, JULIET, Bakersfield. Died Feb 8, 1988, aged 78. Graduate of Stanford University School of Medicine, Stanford, California, 1934. Dr Thorner was a member of the Kern County Medical Society.

WALKER, LIONEL E., Lemoore. Died Nov 10, 1987, aged 60. Graduate of University of Arkansas School of Medicine, Little Rock, 1954. Dr Walker was a member of the Kings County Medical Society.

WHEELER, OWEN W., La Jolla. Died Jan 3, 1988, aged 79. Graduate of Loma Linda University, 1950. Dr Wheeler was a member of the San Diego County Medical Society.

YONAGO, RONALD H., San Jose. Died Dec 11, 1987, aged 54. Graduate of Marquette University, Milwaukee, 1959. Dr Yonago was a member of the Santa Clara County Medical Society.

Utah Medical Association

STEVENSON, J. VICTOR, Salt Lake City. Died Feb 21, 1988, aged 68. Graduate of University of Utah, 1947. Licensed in Utah in 1947. Dr Stevenson was a member of the Salt Lake County Medical Society.

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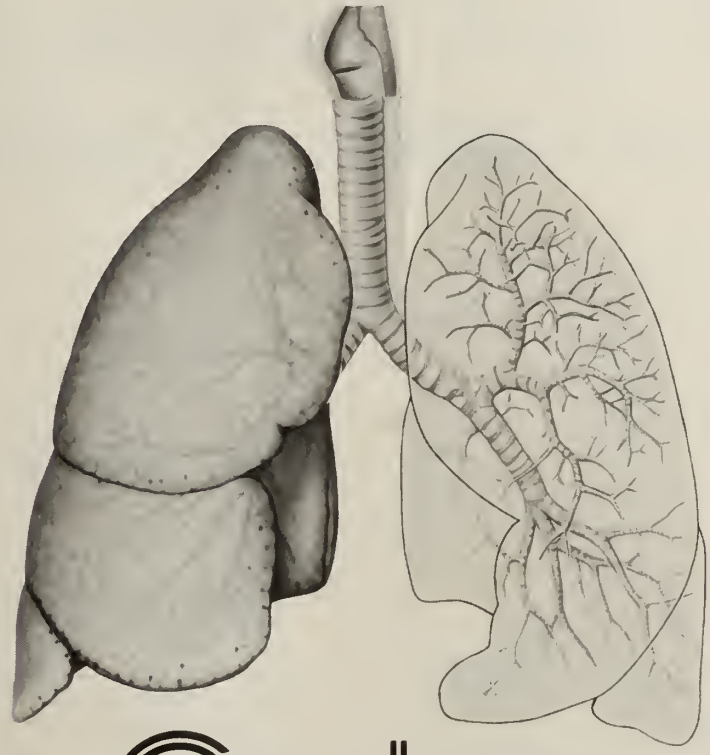

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Haemophilus influenzae and *Streptococcus pneumoniae*
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Note: Ceclor is contraindicated in patients with known allergy to the cephalosporins and should be given cautiously to penicillin-allergic patients.

Penicillin is the usual drug of choice in the treatment and prevention of streptococcal infections, including the prophylaxis of rheumatic fever. See prescribing information.

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Indications: Lower respiratory infections, including pneumonia, caused by *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Streptococcus pyogenes* (group A β-hemolytic streptococci).

Contraindication:
Known allergy to cephalosporins.

Warnings:
CECLOR SHOULD BE ADMINISTERED CAUTIOUSLY TO PENICILLIN-SENSITIVE PATIENTS. PENICILLINS AND CEPHALOSPORINS SHOW PARTIAL CROSS-ALLERGENICITY POSSIBLE REACTIONS INCLUDE ANAPHYLAXIS.

Administer cautiously to allergic patients.

Pseudomembranous colitis has been reported with virtually all broad-spectrum antibiotics. It must be considered in differential diagnosis of antibiotic-associated diarrhea. Colon flora is altered by broad-spectrum antibiotic treatment, possibly resulting in antibiotic-associated colitis.

Precautions:
- Discontinue Ceclor in the event of allergic reactions to it.
- Prolonged use may result in overgrowth of nonsusceptible organisms.
- Positive direct Coombs' tests have been reported during treatment with cephalosporins.
- Ceclor should be administered with caution in the presence of markedly impaired renal function. Although dosage adjustments in moderate to severe renal impairment are usually not required, careful clinical observation and laboratory studies should be made.
- Broad-spectrum antibiotics should be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis.
- Safety and effectiveness have not been determined in pregnancy, lactation, and infants less than one month old. Ceclor penetrates mother's milk. Exercise caution in prescribing for these patients.

Adverse Reactions: (percentage of patients)
Therapy-related adverse reactions are uncommon. Those reported include:
- Gastrointestinal (mostly diarrhea): 2.5%.
- Symptoms of pseudomembranous colitis may appear either during or after antibiotic treatment.
- Hypersensitivity reactions (including morbilliform eruptions, pruritus, urticaria, and serum-sickness-like reactions that have included erythema multiforme [rarely, Stevens-Johnson syndrome] or the above skin manifestations accompanied by arthritis/arthralgia and, frequently, fever): 1.5%; usually subside within a few days after cessation of therapy. Serum-sickness-like reactions have been reported more frequently in children than in adults and have usually occurred during or following a second course of therapy with Ceclor. No serious sequelae have been reported. Antihistamines and corticosteroids appear to enhance resolution of the syndrome.
- Cases of anaphylaxis have been reported, half of which have occurred in patients with a history of penicillin allergy.
- As with some penicillins and some other cephalosporins, transient hepatitis and cholestatic jaundice have been reported rarely.
- Rarely, reversible hyperactivity, nervousness, insomnia, confusion, hypertonia, dizziness, and somnolence have been reported.
- Other: eosinophilia, 2%; genital pruritus or vaginitis, less than 1%; and, rarely, thrombocytopenia.

Abnormalities in laboratory results of uncertain etiology.
- Slight elevations in hepatic enzymes.
- Transient fluctuations in leukocyte count (especially in infants and children).
- Abnormal urinalysis; elevations in BUN or serum creatinine.
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- False-positive tests for urinary glucose with Benedict's or Fehling's solution and Clinitest® tablets but not with Tes-Tape® (glucose enzymatic test strip, Lilly). [061787L]

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CONTINUING MEDICAL EDUCATION

(Continued from Page 538)

August 1-5—**Modern Radiology Practice.** UCSD at Fess Parker Red Lion Resort, Santa Barbara. Mon-Fri. 30 hrs. $425. Contact: Mary J. Ryals and Associates, PO Box 920113, Norcross, GA 30092-0113. (404) 641-9773.

August 22-26—**Radiology: 1988 USC Radiology Summer Hawaiian Seminar.** USC at Kauai Westin, Lihue, Hawaii. Mon-Fri. 28 hrs. $475. Contact: USC.

August 25-28—**Fourth Annual Physics and Biology of Radiology.** UCSD at La Jolla Village Inn. Thurs-Sat. 25 hrs. $395. Contact: Mary J. Ryals and Associates, PO Box 920113, Norcross, GA 30092-0113. (404) 641-9773.

September 9-11—**Fourth Annual Sonography Update and Review Course.** UCSD at Hanalei Hotel, San Diego. Fri-Sun. 17 hrs. $375. Contact: Mary J. Ryals and Associates, PO Box 920113, Norcross, GA 30092-0113. (404) 641-9773.

October 31-November 1—**San Diego Postgraduate Radiology Course.** UCSD at Hotel del Coronada, San Diego. Mon-Tues. 28 hrs. $450. Contact: UCSD.

SURGERY

June 2-3—**17th Annual Neurosurgery Postgraduate Course.** UCSF at Hyatt Regency, San Francisco. Thurs-Fri. 16 hrs. $325. Contact: UCSF.

June 20-23—**First International Symposium on Orbital Plastic Surgery.** Plastic Surgery Education Foundation at Westin St Francis Hotel, San Francisco. Mon-Thurs. 25 hrs. $600. Contact: PSEF, 233 N. Michigan Ave, Ste 1900, Chicago, Illinois 60601. (312) 856-1818.

August 18-21—**Discussions of Current Hand Care Concepts.** Plastic Surgery Education Foundation at San Diego. Thurs-Sun. Contact: PSEF, 233 N. Michigan Ave, Suite 1900, Chicago, Illinois 60601.

September 17—**Summary of Clinical Use of Argon, YAG and CO2 Lasers for Cutaneous Lesions.** Palo Alto Medical Foundation at Palo Alto Medical Clinic. Sat. 6 hrs. Contact: Palo Alto Medical Clinic, 300 Homer Ave, Palo Alto 94301. (415) 321-4121.

October 14-15—**13th Annual Clinical Neurosciences Symposium.** Dominican Neurologic Institute at Chaminade Conference Center, Santa Cruz. Fri-Sat. 11 hrs. $350. Contact: Karen Rickenbach, DNI Dominican Hospital, 1555 Soquel Dr, Santa Cruz 95065. (408) 462-7562.

OF INTEREST TO ALL PHYSICIANS

May 15-20—**Primary Care Medicine: Update '88.** UCSF at the Waiohai Hotel, Hawaii. Sun-Fri. 20 hrs. $425. Contact: UCSF.

May 19-22—**AGS/AFAR: Annual Meeting.** American Geriatrics Society at Disneyland Hotel, Anaheim. Thurs-Sun. $125. Contact: American Geriatrics Society, 770 Lexington Ave, Ste 400, New York, NY 10021. (212) 308-1414.

May 26-27—**Current Concepts of Anatomic Pathology.** UCSF. Thur-Fri. Contact: UCSF.

May 31-June 4—**Family Practice Refresher Course.** UCLA at the Miramar-Sheraton Hotel, Santa Monica. Tues-Sat. 36 hrs. $395. Contact: UCLA.

June 2—**Public Lecture Series on Aging.** UCLA at the Westwood Methodist Church, Los Angeles. Thurs. $10. Contact: UCLA.

June 6-10—**Occupational Respiratory Protection.** USC. 4 hrs. Contact: Institute of Safety and Systems Management, 3500 S. Figueroa St., Ste. 202, Los Angeles, 90007. (213) 743-6523.

June 8—**AIDS.** Loma Linda University. Wed. $65. Contact: LLU.

June 11-12—**Procedure Skills for Primary Care Physicians.** Current Concept Seminars at Ibus Hotel, Milbrae. Sat-Sun. Contact: Donald Berman, MD, Current Concept Seminars, 3301 Johnson St, Hollywood, Florida 33021. (305) 966-1009.

June 11-12—**Lactation Educator Program.** UCLA. Sat-Sun. 26 hrs. $525. Contact: UCLA.

June 12-17—**12th Annual FINGERS TO THE TOES: Comprehensive and Practical Orthopaedics for Primary Care and Emergency Medicine.** UCD at Stanford Sierra Camp, Fallen Leaf Lake. Sun-Fri. 36 hrs. $420. Contact: UCD.

June 13-14—**Ergonomics: Building Efficiency and Safety in the Workplace.** USC. Mon-Tues. 2 hrs. Contact: Institute of Safety and Systems Management, 3500 S. Figueroa St., Ste. 202, Los Angeles, 90007. (213) 743-6523.

June 13-17—**Family Practice Refresher Course.** UCI at Sheraton Newport, Newport Beach. Mon-Fri. 44.5 hrs. $575. Contact: UCI.

June 13-18—**UCI Family Practice Refresher Course.** UCI and Memorial Medical Center at Sheraton Newport Hotel, Newport Beach. Mon-Sat. Contact: Memorial Medical Center, PO Box 1428, Long Beach 90801-1428. (213) 595-3811.

June 14-17—**Society of Nuclear Medicine Annual Meeting.** SNM at Moscone Convention Center, San Francisco. Contact: SNM, 475 Park Ave. S., New York, 10016. (212) 889-0717.

June 15-16—**AIDS/ARC: Update 1988.** UCSF at the Civic Auditorium, San Francisco. Fri-Sat. Contact: UCSF.

June 18-19—**Skills Workshop: Flexible Sigmoidoscopy and Colposcopy.** UCI at Sheraton Newport, Newport Beach. Sat-Sun. 16 hrs. $140-ea., $250-both. Contact: UCI.

June 22-24—**A Journey to Clarity: Symposium for the Exploration and Integration of the Issues in the Recovery Process.** Monterey Community Hospital at Monterey Conference Center. Wed-Fri. $250. Contact: Nomi Feldman, Conference Coordinator, 3770 Tansy St, San Diego 92121. (619) 453-6222.

June 25-26—**10th Annual Poison Control Center Symposium on Toxicology and Poisoning.** UCSF and Continuing Medical Education in Pharmacy at San Francisco. Sat-Sun. 14 hrs. $235. Contact: Continuing Education S/P, UCSF, Box 0446, San Francisco 94143. (415) 476-4194.

July 14-17—**Decentralized Care of People With AIDS: An Educational Seminar for Developmental Approach.** Sonoma County Academic Foundation for Excellence at Flamingo Hotel, Santa Rosa. Thurs-Sun. $275. Contact: Mary Ellen Buechter, SCAFE, 3325 Chanate Rd, Santa Rosa, 95404. (707) 527-4121.

July 15-18—**Caring for People With AIDS and Their Loved Ones.** Concern for Dying: an Educational Council, at Bishop's Ranch, Healdsburg. Fri-Mon. Contact: Penny Weingarten, 250 West 57th St., Room 831, New York, NY 10107. (800) 248-2122.

July 25-29—**SPORTS MEDICINE 1988: A Practical Approach to Caring for Today's Athletes.** UCSD at San Diego Princess. Mon-Fri. 23 hrs. Contact: UCSD.

July 27-31—**Wilderness Medicine '88.** Wilderness Medical Society at Squaw Valley, Lake Tahoe. Wed-Sun. 22 hrs. Contact: Jackie Silva, Coordinator, Mountain Medical Seminars, PO Box 321, Yreka, 96097. (916) 842-4667.

August 1-3—**4th International ND: YAG Laser Symposium.** International Laser Foundation at Sheraton Universal Hotel, Los Angeles. Mon-Wed. Contact: ILF, 3960 Park Blvd, Ste E, San Diego 92103. (619) 692-9115.

August 3-6—**15th Annual Meeting: The Peruvian American Medical Society** at Westin Bonaventure Hotel, Los Angeles. Wed-Sat. Contact: Hugo Ortiz, MD, Chairman, Scientific Program, 6488 Tamerlane Dr, West Bloomfield, MI 48322.

August 12-14—**Diagnosis and Management of Respiratory Diseases.** Medical Education Resources at Doubletree Inn, Monterey. Fri-Sun. $225. Contact: Deborah Wilderson, MER, 5808 S. Rapp St, Ste 202, Littleton, CO 80120. (800) 421-3756.

August 13-20—**8th Annual Symposium on Fine Needle Aspiration.** UCSF at Kaanapali Beach, Maui. 1 week. 25 hrs. Contact: UCSF.

September 15-18—**Decentralized Care of People With AIDS: An Educational Seminar for Developmental Approach.** Sonoma County Academic Foundation for Excellence at Flamingo Hotel, Santa Rosa. Thurs-Sun. $275. Contact: Mary Ellen Buechter, SCAFE, 3325 Chanate Rd, Santa Rosa, 95404. (707) 527-4121.

September 28-30—**Primary Care Medicine: Principles and Practice.** UCSF at the Portman Hotel, San Francisco. Wed-Fri. $365. Contact: UCSF.

October 10-14—**Current Topics in Occupational Medicine.** UCSF at Cathedral Hill Hotel, San Francisco. Mon-Fri. 40 hrs. $550. Contact: UCSF.

October 20-22—**Recent Advances in Pulmonary and Critical Care Medicine.** UCSF at Mark Hopkins Hotel, San Francisco. Thurs-Sat. 15 hrs. $365. Contact: UCSF.

November 11-14—**The Spine: Current Concepts of Diagnosis and Treatment.** Spine Study Group at Marriott Desert Springs Resort, Palm Springs. Fri-Mon. $250. Contact: Spine Study Group, PO Box 33185, San Diego 92103. (619) 692-9115.

(Continued on Page 603)

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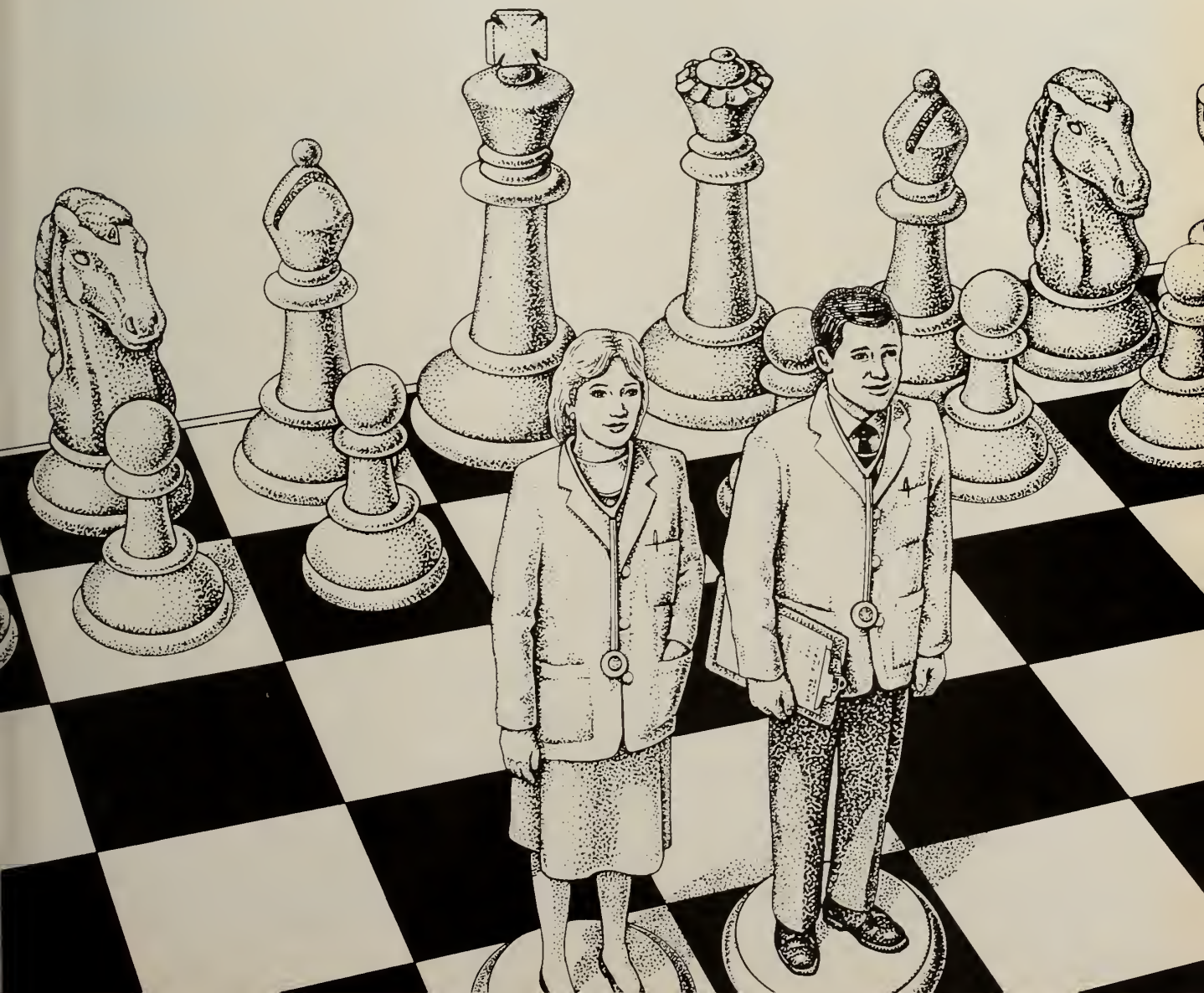

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EMERGENCY MEDICINE. We are an established 35 physician partnership in northern California and we are seeking BE/BC Emergency Physicians to join us. All of our facilities have moderate volumes, many serve as EMS base-stations. Salary and benefits are competitive; malpractice is paid. If interested in a career in Emergency Medicine with us, please contact Sacramento Emergency Medical Group, 4325 Auburn Blvd, Ste 100, Sacramento, CA 95841; (916) 486-4414.

FAMILY PRACTITIONER. Visalia Medical Clinic has an opening for a BC/BE Family Practitioner to join a four physician department. Located in the San Joaquin Valley of California, serving a market area of approximately 350,000 citizens, the Visalia Medical Clinic is a 40 physician multispecialty clinic. Excellent hospital services and facilities. Compensation is incentive oriented with advancement to full partnership after one year. Excellent fringe benefits. John G. Heinsohn, Administrator, 5400 W. Hillsdale, Visalia, CA 93291; (209) 733-5222.

NEAR STANFORD. Six Internists, all subspecialty trained and members of clinical faculty at Stanford, interested in an Associate with subspecialty interest and training. Should be well grounded in Internal Medicine. Send CV to Dr Bigler, El Camino Internal Medical Group, 125 South Dr, Mountain View, CA 94040.

CRESCENT CITY, CALIFORNIA. Exciting position available at a growing 24,000 visit ER in a rural, coastal community. Fee-for-service with possibility of six figure income. Send CV to Art B. Wong, MD, FACEP, 1 Maritime Plaza, Ste 710, San Francisco, CA 94111.

NEUROSURGERY. Visalia Medical Clinic has an opening for a BC/BE Neurological Surgeon to enter an immediate and active practice. Located in the San Joaquin Valley of California, serving a market area of approximately 350,000 citizens. Two Neurosurgeons presently serving this area. Excellent hospital services and facilities. Must be BC/BE. Compensation is incentive oriented with advancement to full partnership after one year. Excellent fringe benefits. John G. Heinsohn, Administrator, 5400 W. Hillsdale, Visalia, CA 93291; (209) 733-5222.

PHYSICIANS WANTED

OB/GYN. Multispecialty group in northwest Washington desires second Obstetrician. Excellent practice opportunity, full range of benefits, early partnership status, all practice costs paid. For more information contact Shane Spray, Administrator, 1400 E. Kincaid, Mount Vernon, WA 98273; (206) 428-2524.

PHYSICIANS WANTED IN TEXAS AND OKLAHOMA. Cardiology, Cardiovascular Surgery, Dermatology, ENT, Family Practice, General Surgery, Internal Medicine, OB/GYN, Orthopedic Surgery, Pulmonology, Urology. Excellent quality of life, first year guarantee, etc. Other opportunities available also. Reply with CV or call Armando L. Frezza, Medical Support Services, 8806 Balcones Club Dr, Austin, TX 78750; (512) 331-4164.

SOUTH CENTRAL WYOMING. Immediate practice opportunity for BC/BE Urologist. Well-equipped JCAH hospital for a service area of approximately 20,000 population. No state or city income tax. Relocation incentives. Superior hunting, fishing, camping, snowmobiling. Three hours to Colorado ski area, five hours to Jackson Hole. One and one-half hours to the mountains. If interested, please send CV and references to D. Abels, DO, Chairman, Recruiting Committee or Richard Mills, Executive Director, Memorial Hospital of Carbon County, Rawlins, WY 82301; (307) 324-2221.

ARIZONA-BASED PHYSICIAN recruiting firm has opportunities coast-to-coast. "Quality Physicians for Quality Clients since 1972." Call (602) 990-8080; or send CV to Mitchell & Associates, Inc, PO Box 1804, Scottsdale, AZ 85252.

DERMATOLOGIST. Visalia Medical Clinic has an opening for a BC/BE Dermatologist now staffed by one physician who has been with the Clinic for 15 years. Located in the San Joaquin Valley in central California and population approximately 350,000. Progressive city of 62,000, near national parks and the ocean. Compensation is incentive oriented with advancement to full partnership after one year. Excellent fringe benefits. If interested, CV to John G. Heinsohn, Administrator, 5400 W. Hillsdale, Visalia, CA 93291; (209) 733-5222.

PHYSICIANS WANTED

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NORTHERN CALIFORNIA

Several positions available for Family Practice, Internal Medicine, and most subspecialties. We are a young aggressive group in a well known HMO organization with excellent benefits and a very reasonable call schedule. You will enjoy the patient population with ample time to enjoy the mountains and San Francisco which are nearby. If interested please call or send CV to Physician Recruitment, Administration, Kaiser Permanente Medical Group, Inc, 1305 Tommydon St, Stockton, CA 95210; (209) 476-3300.

FAMILY PRACTICE in four season playground. Live, work, and play in beautiful north Idaho. Excellent professional opportunity. Private practice affiliated with JCAH accredited hospital. For details call Nancy collect at (208) 784-1221, ext 304. Shoshone Medical Center, Jacobs Gulch, Kellogg, ID 83837.

CALIFORNIA, SONORA. Staff Physician position available in 11-12,000 visit ER in quaint, historic, growing gold country community with fantastic recreational opportunities, one hour from Yosemite. Excellent opportunity in an academic and democratic group. Send CV to Art B. Wong, MD, FACEP, EPMG, 1 Maritime Plaza, Ste 710, San Francisco, CA 94111.

PHYSICIANS WANTED. A General Surgeon and an Oncologist to join 16 physician multispecialty group with attached 40-bed hospital located in southern Idaho. Contact Business Administrator, Box 1233, Twin Falls, ID 83301.

FAMILY PHYSICIAN. BC/BE to join the Family Practice department of a busy, primary care based multispecialty group. Excellent opportunity for growth. Contact Shane Spray, Administrator, Skagit Valley Medical Center, 1400 E. Kincaid, Mt. Vernon, WA 98273; (206) 428-2524.

PEDIATRICIAN position available with multispecialty group; BE/BC required; strong incentive plan; benefits included; retirement program and located in San Luis Obispo, California on the central coast. Send CV to Administration/Recruitment, San Luis Medical Clinic, 1235 Osos St, San Luis Obispo, CA 93401.

OBSTETRICIAN/GYNECOLOGIST position available with multispecialty group; BE/BC required; strong incentive plan; benefits included; retirement program and located in San Luis Obispo, California on the central coast. Send CV to Administration/Recruitment, San Luis Medical Clinic, 1235 Osos St, San Luis Obispo, CA 93401.

CENTRAL OREGON community seeks BE/BC Internist. 103-bed combination facility has ICU/CCU. Service area of 12,000. Coverage available by Internal Medicine group in neighboring town. Generous practice assistance package. An outdoorsman's winter and summer paradise! Contact Jean Erickson, PROSEARCH, 305 NE 102nd Ave, Portland, OR 97220; (503) 256-2070.

(Continued on Page 608)

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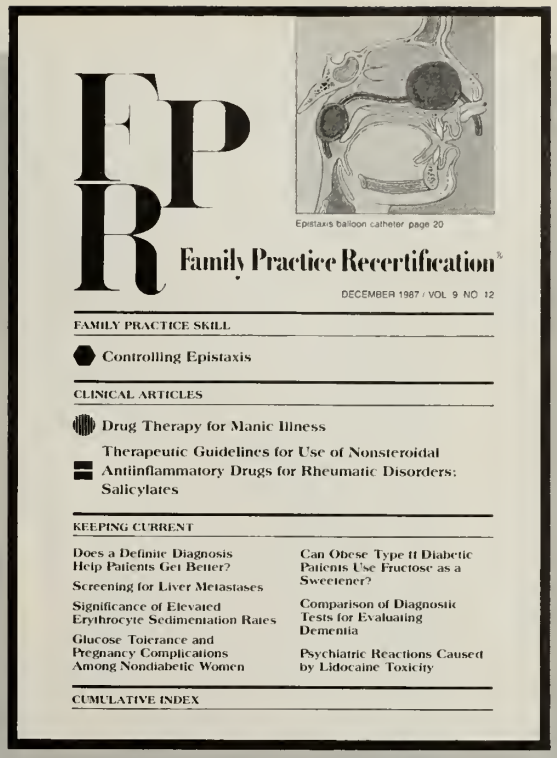
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Epistaxis balloon catheter page 20
Family Practice Recertification
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CONTINUING MEDICAL EDUCATION

(Continued from Page 600)

November 10-13—**Sexual Literacy: What is it? What do we know? What do we need to know? Whose responsibility is it?** The Society for the Scientific Study of Sex at the Cathedral Hill Hotel, San Francisco. Thurs-Sun. Contact: Bernard Goldstein, San Francisco State University, Biology Dept., 1600 Holloway Ave., San Francisco, 94132. (415) 338-1548.

IDAHO

June 3—**Managing Major Radiation Accidents.** Idaho Falls Medical Society at University Place, Idaho Falls. Fri. 7 hrs. Contact: Kearny Poser, Idaho Falls Medical Society, 6991 Limousin Ave, Idaho Falls 83404. (208) 524-6370.

July 21-23—**Idaho Medical Association Annual Meeting.** Sun Valley. Thurs-Sat. Contact: IMA, 305 W. Jefferson, PO Box 2668, Boise 83701. (208) 344-7888.

August 29-30—**Northwest Regional Perinatal Conference—Current Issues in Ob/Gyn, Neonatology and Pediatrics.** Inland Empire Perinatal Center at Coeur d'Alene Resort. Contact: Inland Empire Perinatal Center, 411 Medical Center Bldg, Spokane, WA 99204. (509) 624-3182

MONTANA

September 29-October 1—**Montana Medical Association Annual Meeting.** Heritage Inn, Great Falls. Fri-Sat. Contact: MMA, 2012 11th Ave., Suite 12, Helena 59601. (406) 443-4000.

NEW MEXICO

Information, requests for accreditation and items to be listed should be sent to the chairman of the CME Committee, New Mexico Medical Society, 303 San Mateo NE, Suite 204, Albuquerque, NM 87108 at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 266-7868.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

May 17-22—**Basic Course in Otolaryngic Allergy.** Holiday Inn, Journal Center, Albuquerque. Tues-Sun. Contact: American Academy of Otolaryngic Allergy Foundation, 1101 Vermont, NW, Washington, DC 20005.

May 19-20—**Mental Health Services With Hispanic and Native American Children and Families.** Thurs-Fri. Contact: UNM SOM, Office of CME, (505) 277-3942.

June 2-3—**8th Annual UNM/ACEP Emergency Medicine Symposium.** AMFAC Hotel, Albuquerque. Thurs-Fri. Contact: UNM SOM, Office of CME, (505) 277-3942.

June 3—**Ethical Concerns in the Practice of Medicine—1988.** Memorial General Hospital, Las Cruces. Fri. Contact: Office of Medical Affairs, (505) 521-2218. •

(Continued on Page 606)

WHEN ACID REFLUX ERUPTS

Zantac dramatically lessens pain of acid reflux[1] by inhibiting the formation of acid at its source–an action unique among pharmaceutical agents indicated for the treatment of gastroesophageal reflux disease.

Zantac® Tablets

ranitidine HCl/Glaxo 150 mg tablets bid

The only H_2-antagonist indicated for the treatment of gastroesophageal reflux disease

1 Sontag S, Robinson M, McCallum R, et al. Ranitidine therapy for gastroesophageal reflux disease: Results of a large double blind trial. *Arch Intern Med* 1987; 147:1485–1491.

See next page for Brief Summary of Product Information

Glaxo/ ROCHE

ZANTAC® 150 Tablets
(ranitidine hydrochloride)
ZANTAC® 300 Tablets
(ranitidine hydrochloride)

BRIEF SUMMARY

The following is a brief summary only. Before prescribing, see complete prescribing information in ZANTAC® product labeling.

INDICATIONS AND USAGE: ZANTAC® is indicated in:
1. Short-term treatment of **active duodenal ulcer.** Most patients heal within four weeks.
2. **Maintenance therapy** for duodenal ulcer patients at reduced dosage after healing of acute ulcers.
3. The treatment of **pathological hypersecretory conditions** (eg, Zollinger-Ellison syndrome and systemic mastocytosis).
4. Short-term treatment of **active, benign gastric ulcer.** Most patients heal within six weeks and the usefulness of further treatment has not been demonstrated.
5. Treatment of **gastroesophageal reflux disease (GERD).** Symptomatic relief commonly occurs within one or two weeks after starting therapy. Therapy for longer than six weeks has not been studied.

In active duodenal ulcer; active, benign gastric ulcer; hypersecretory states, and GERD, concomitant antacids should be given as needed for relief of pain.

CONTRAINDICATIONS: ZANTAC® is contraindicated for patients known to have hypersensitivity to the drug.

PRECAUTIONS: General: 1. Symptomatic response to ZANTAC® therapy does not preclude the presence of gastric malignancy.
2. Since ZANTAC is excreted primarily by the kidney, dosage should be adjusted in patients with impaired renal function (see **DOSAGE AND ADMINISTRATION**). Caution should be observed in patients with hepatic dysfunction since ZANTAC is metabolized in the liver.

Laboratory Tests: False-positive tests for urine protein with Multistix® may occur during ZANTAC therapy, and therefore testing with sulfosalicylic acid is recommended.

Drug Interactions: Although ZANTAC has been reported to bind weakly to cytochrome P-450 in vitro, recommended doses of the drug do not inhibit the action of the cytochrome P-450-linked oxygenase enzymes in the liver. However, there have been isolated reports of drug interactions which suggest that ZANTAC may affect the bioavailability of certain drugs by some mechanism as yet unidentified (eg, a pH-dependent effect on absorption or a change in volume of distribution).

Carcinogenesis, Mutagenesis, Impairment of Fertility: There was no indication of tumorigenic or carcinogenic effects in lifespan studies in mice and rats at doses up to 2,000 mg/kg/day.

Ranitidine was not mutagenic in standard bacterial tests (*Salmonella, E coli*) for mutagenicity at concentrations up to the maximum recommended for these assays.

In a dominant lethal assay, a single oral dose of 1,000 mg/kg to male rats was without effect on the outcome of two matings per week for the next nine weeks.

Pregnancy: ***Teratogenic Effects: Pregnancy Category B:*** Reproduction studies have been performed in rats and rabbits at doses up to 160 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to ZANTAC. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers: ZANTAC is secreted in human milk. Caution should be exercised when ZANTAC is administered to a nursing mother.

Pediatric Use: Safety and effectiveness in children have not been established.

Use in Elderly Patients: Ulcer healing rates in elderly patients (65 to 82 years of age) were no different from those in younger age groups. The incidence rates for adverse events and laboratory abnormalities were also not different from those seen in other age groups.

ADVERSE REACTIONS: The following have been reported as events in clinical trials or in the routine management of patients treated with oral ZANTAC®. The relationship to ZANTAC therapy has been unclear in many cases. Headache, sometimes severe, seems to be related to ZANTAC administration.

Central Nervous System: Rarely, malaise, dizziness, somnolence, insomnia, and vertigo. Rare cases of reversible mental confusion, agitation, depression, and hallucinations have been reported, predominantly in severely ill elderly patients. Rare cases of reversible blurred vision suggestive of a change in accommodation have been reported.

Cardiovascular: Rare reports of tachycardia, bradycardia, and premature ventricular beats.

Gastrointestinal: Constipation, diarrhea, nausea/vomiting, and abdominal discomfort/pain.

Hepatic: In normal volunteers, SGPT values were increased to at least twice the pretreatment levels in 6 of 12 subjects receiving 100 mg qid IV for seven days, and in 4 of 24 subjects receiving 50 mg qid IV for five days. With oral administration there have been occasional reports of reversible hepatitis, hepatocellular or hepatocanalicular or mixed, with or without jaundice.

Musculoskeletal: Rare reports of arthralgias.

Hematologic: Reversible blood count changes (leukopenia, granulocytopenia, thrombocytopenia) have occurred in a few patients. Rare cases of agranulocytosis or of pancytopenia, sometimes with marrow hypoplasia, have been reported.

Endocrine: Controlled studies in animals and man have shown no stimulation of any pituitary hormone by ZANTAC (ranitidine hydrochloride) and no antiandrogenic activity, and cimetidine-induced gynecomastia and impotence in hypersecretory patients have resolved when ZANTAC has been substituted. However, occasional cases of gynecomastia, impotence, and loss of libido have been reported in male patients receiving ZANTAC, but the incidence did not differ from that in the general population.

Integumentary: Rash, including rare cases suggestive of mild erythema multiforme, and rarely, alopecia.

Other: Rare cases of hypersensitivity reactions (eg, bronchospasm, fever, rash, eosinophilia) and small increases in serum creatinine.

OVERDOSAGE: Information concerning possible overdosage and its treatment appears in the full prescribing information.

DOSAGE AND ADMINISTRATION: Active Duodenal Ulcer: The current recommended adult oral dosage is 150 mg twice daily. An alternate dosage of 300 mg once daily at bedtime can be used for patients in whom dosing convenience is important. The advantages of one treatment regimen compared to the other in a particular patient population have yet to be demonstrated.

Maintenance Therapy: The current recommended adult oral dosage is 150 mg at bedtime.

Pathological Hypersecretory Conditions (such as Zollinger-Ellison syndrome): The current recommended adult oral dosage is 150 mg twice a day. In some patients it may be necessary to administer ZANTAC® 150-mg doses more frequently. Doses should be adjusted to individual patient needs, and should continue as long as clinically indicated. Doses up to 6 g/day have been employed in patients with severe disease.

Benign Gastric Ulcer: The current recommended adult oral dosage is 150 mg twice a day.

GERD: The current recommended adult oral dosage is 150 mg twice a day.

Dosage Adjustment for Patients with Impaired Renal Function: On the basis of experience with a group of subjects with severely impaired renal function treated with ZANTAC, the recommended dosage in patients with a creatinine clearance less than 50 ml/min is 150 mg every 24 hours. Should the patient's condition require, the frequency of dosing may be increased to every 12 hours or even further with caution. Hemodialysis reduces the level of circulating ranitidine. Ideally, the dosage schedule should be adjusted so that the timing of a scheduled dose coincides with the end of hemodialysis.

HOW SUPPLIED: ZANTAC® 300 Tablets (ranitidine hydrochloride equivalent to 300 mg of ranitidine) are yellow, capsule-shaped tablets embossed with "ZANTAC 300" on one side and "Glaxo" on the other. They are available in bottles of 30 (NDC 0173-0393-40) and unit dose packs of 100 tablets (NDC 0173-0393-47).

ZANTAC® 150 Tablets (ranitidine hydrochloride equivalent to 150 mg of ranitidine) are white tablets embossed with "ZANTAC 150" on one side and "Glaxo" on the other. They are available in bottles of 60 tablets (NDC 0173-0344-42) and unit dose packs of 100 tablets (NDC 0173-0344-47).

Store between 15° and 30°C (59° and 86°F) in a dry place. Protect from light. Replace cap securely after each opening.

August 1987

Glaxo

Glaxo Inc.
Research Triangle Park, NC 27709

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CONTINUING MEDICAL EDUCATION

(Continued from Page 603)

July 7-9—**New Mexico Ophthalmological Society Annual Meeting.** Eldorado Hotel, Santa Fe. Thurs-Sat. Contact: Donald J. Ham, MD, 1124 10th, Alamogordo 88310. (505) 434-1200.

July 18-21—**Ruidoso Family Practice Seminar.** Inn of the Mountain Gods, Mescalero. Mon-Thurs. Contact: NM Chapter, AAFP, PO Box 23070, Albuquerque 87192. (505) 298-5300.

July 22-24—**Diagnosis and Management of Arrhythmia.** Presbyterian Heart Institute, Albuquerque. Fri-Sun. Contact: Barry Ramo, MD, (505) 841-1065/(505) 242-2796.

July 28-30—**General Surgical Update.** Hilton Hotel, Albuquerque. Thurs-Sat. Contact: UNM SOM, Office of CME, (505) 277-3942.

August 5-6—**Santa Fe Cardiology Update.** Fri-Sat. Contact: New Heart Program, (505) 255-8474.

September 8-10—**Concepts & Controversies in Perinatal Care.** Albuquerque. Thurs-Sat. Contact: UNM SOM, Office of CME, (505) 277-3942.

September 22-24—**Primary Care Update '88.** UNM Conference Center, Albuquerque. Thurs-Sat. Contact: UNM SOM, Office of CME, (505) 277-3942.

October 6-8—**Management of Radiation Accidents.** Sheraton Old Town Hotel, Albuquerque. Thurs-Sat. Contact: UNM SOM, Office of CME, (505) 277-3942.

October 18-21—**Epidemiologic & Methodologic Problems in Determining Nutritional Status of Older Persons.** Sheraton Old Town Hotel, Albuquerque. Tues-Fri. Contact: UNM SOM, Office of CME, (505) 277-3942.

October 28-29—**New Mexico Medical Society Interim Meeting** and **Loss Control Seminar,** Physicians Mutual Liability Insurance Co. Journal Center Pyramid Holiday Inn, Albuquerque. Fri-Sat. Contact: New Mexico Medical Society, 303 San Mateo NE, Albuquerque 87108. (505) 266-7868.

November 11—**New Mexico Pediatric Society.** Inn of the Mountain Gods, Ruidoso. Fri. Contact: Marilyn Stark, (505) 265-7431.

December 1-3—**American College of Physicians—New Mexico Scientific Meeting.** Hilton Hotel, Albuquerque. Thurs-Sat. Contact: UNM SOM, Office of CME, (505) 277-3942.

December 9-10—**Trauma Update '88.** Clarion Four Seasons Hotel, Albuquerque. Fri-Sat. Contact: UNM SOM, Office of CME, (505) 277-3942.

UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the CME office of the Utah Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. They also must meet the definition of Utah Approved CME Credit for the purpose of medical license reregistration in Utah. Accredited institutions wishing to list AMA Category 1/Utah Approved CME courses here should send information at least two months in advance to the Office of Continuing Medical Education, 540 East Fifth South, Salt Lake City, Utah 84102; or phone (801) 355-5290. For information on CME accreditation or on the CME requirements of the Utah Physicians' Licensing Board, please write the CME office at the above address.

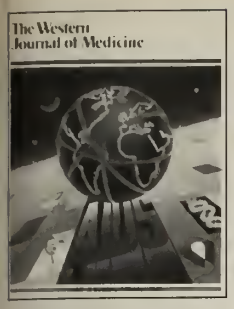
NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution or the CME office for current details.

MEDICAL GRAND ROUNDS

Each Wed—8:00-9:00 a.m. Alternating between University of Utah Medical Center and VA Medical Center, Salt Lake City. Contact: William D. Odell, MD, PhD, Professor and Chairman, Dept of Internal Medicine, Univ of Utah, (801) 581-7606.

(Continued on Page 609)

SPECIAL ISSUES



AIDS—A Global Perspective

The short and remarkable history of AIDS epidemiology began in 1981 with the description of the clinical syndrome in California and New York. In the 6 years that have followed, intensive epidemiologic studies have defined the mode of spread of AIDS and laid the foundation for current control efforts. Serosurveys and retrospective clinical studies have been used to trace the temporal origins of the pandemic prior to 1981, while prospective studies and an increasingly comprehensive worldwide surveillance system have provided more accurate data for the years following 1981. AIDS cases have now been reported and investigated throughout the world.

This issue, from the Special Programme on AIDS of the World Health Organization, considers the methods and limitations of AIDS case reporting and HIV serologic studies, summarizes modes of HIV transmission, defines geographic patterns of spread, and examines the epidemiology of HIV infections by continent.

—Jonathan M. Mann, MD
Director,
Special Programme on AIDS
World Health Organization,
Geneva

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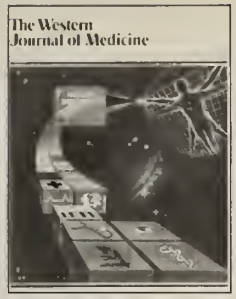

Medical Informatics

I would suggest that the computer in its relation to medicine is analogous to that of the microscope in the last century. . . . The analogous role that I believe the computer is now taking on is also that of a breakthrough tool—one enabling us to explore and better understand the informational and cognitive foundations of medicine. Its application to the classification and retrieval of data and to the management of information will result in a deeper insight into the structure of medical information and knowledge itself.

—Marsden S. Blois, PhD, MD

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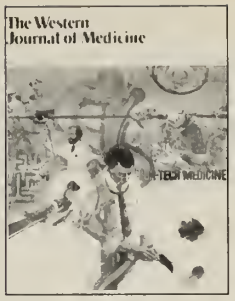

High-Tech Medicine

Progress in medical science seems to come in rushes. There are long periods of time during which we mainly fine-tune the status quo: third-generation drugs, better optics for endoscopes, more accurate assays, rapid development of x-ray film and so forth. Then, out of nowhere, a surge of new discoveries whose potential applications to medical practice seem limitless takes our breath away. We are now in such an epoch. Powerful and precise lasers. Almost unbelievable organ transplantation. Complex and uniquely informative magnetic resonance imaging and positron emission tomography. Exquisitely specific monoclonal antibodies. And the immense potential of modern molecular biology. This rush of new advances, collapsed into such a brief period of time, boggles the mind.

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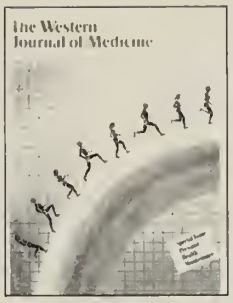

Personal Health Maintenance

The goal of this special issue is to provide an authoritative, current guide to disease prevention and health promotion. The contributors are distinguished experts in public health, epidemiology and clinical medicine.

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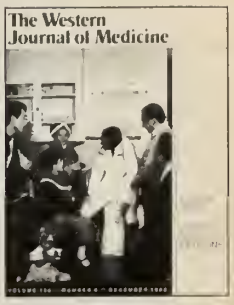

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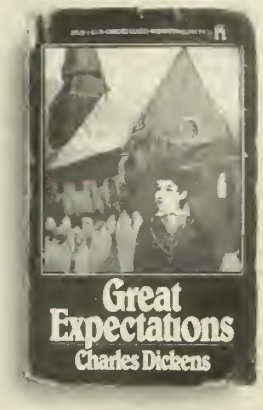

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(Continued from Page 602)

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FAMILY PHYSICIANS sought to join established physicians or develop solo practices in prosperous communities in New Mexico and Colorado. Please submit CV to Rita Longino, Southwest Community Health Services, PO Box 26666, Albuquerque, NM 87125-6666; or call 1 (800) 545-4030, ext 8300.

GENERAL PRACTICE. Busy medical center needs full-time physicians for urgent appointments. Significant evening and weekend hours. Abundant free time with no on-call responsibility. Excellent benefits and retirement program. Kaiser Permanente, Santa Teresa Hospital, 250 Hospital Pkwy, San Jose, CA 95119; (408) 972-6180.

PRIMARY CARE, INTERNIST, OR FAMILY PRACTITIONER who is BC/BE for satellite clinic in a rural community 30 minutes from main clinic, which is a 35 physician multispecialty group. Guaranteed income plus excellent benefits. No investment required. Send CV to Search Committee, Walla Walla Clinic, 55 W. Tietan, Walla Walla, WA 99362.

GASTROENTEROLOGIST. Second Gastroenterologist wanted for rapidly growing HMO in northern California wine country. Send CV to Richard Permutt, MD, Permanente Medical Group, 401 Bicentennial Way, Santa Rosa, CA 95403-2192.

INTERNAL MEDICINE. BC/BE Internist to associate with three other BC Internists in central California. No investment necessary. Minimal guarantee. Eventual loose partnership sharing personnel and expenses and call. Position available June 1, 1988. Excellent community for family life and unlimited recreation. Rapidly growing, stable economy. Send CV to Number 96, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

GRANTS PASS, OREGON. Seeking BC/BE Family Practitioner to assume well-established Family Practice. Includes OB. Share call with four BC Family Practitioners. Located in all-American city on the Rogue River in southern Oregon. Contact Dan Gleffe, MD, 1587 NW Washington Blvd, Grants Pass, OR 97526; (503) 476-0801.

GENERAL INTERNIST—IDAHO. BE/BC to join four established Internists in primary care/consultation practice with wide variety of intensive care. Excellent public school system and four-year college. Immediate opening. Send CV to CIMPA, 222 E. Elm St, Caldwell, ID 83605.

INTERNIST BC/BE to be second Internist in a satellite of a 36 physician multispecialty clinic. Guaranteed salary and immediate full participation in incentive program. Excellent benefit package and excellent recreational, cultural, and educational opportunities. Send CV to Search Committee, Walla Walla Clinic, 55 W. Tietan, Walla Walla, WA 99362.

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PHYSICIANS WANTED

CARDIOLOGIST, NON-INVASIVE, BC/BE to join six physician group in the Portland metropolitan area—one Cardiologist, one Hematologist/Oncologist, two Gastroenterologists, two Internists. Send CV to Hudson's Bay Medical Group, Inc, PS, 2102 E. McLoughlin Blvd, Vancouver, WA 98661; (206) 695-1334.

PSYCHIATRIST. Knoxville VA Medical Center is actively recruiting for a staff Psychiatrist (full or part-time). Our center has four acute General Psychiatry units, chemical dependency treatment program, therapeutic living unit. If you want to work in a peaceful, relaxed community and get that hometown feeling, then Knoxville is the place for you. Excellent salary and benefits, including attractive retirement plan, 30 days paid vacation, health and life insurance, thrift savings plan (similar to 401K), and malpractice coverage. Require licensure any state. EOE. Contact Chief of Staff (11), VA Medical Center, 1515 W. Pleasant, Knoxville, IA 50138; (515) 842-3101, ext 6006.

SAN FRANCISCO BAY AREA. Multiracial community clinic full-time BC/BE Family Practitioner/Primary Care Internist to join three MDs and six Physician Assistants in providing high quality care to an underserved population. Send CV to Medical Director, Martin Luther King Jr Clinic, 101 Broadway, Richmond, CA 94804.

CALIFORNIA, SAN FRANCISCO BAY AREA. Full-time career Emergency Physician wanted for high volume Emergency Department. Emergency Medicine Board certified or Board-ready mandatory to participate in a group of twenty full-time staff physicians seeing over 300 patients per day. Salaried position, excellent benefits include three weeks paid vacation, one week CME, paid malpractice, health and life insurance, corporate shareholdership in three years. Send CV or contact David Gallagher, MD, 27400 Hesperian Blvd, Hayward, CA 94545.

INTERNIST, BC/BE to join six physician group in Portland metropolitan area—one Cardiologist, one Hematologist/Oncologist, two Gastroenterologists, two Internists. Send CV to Hudson's Bay Medical Group, Inc, PS, 2102 E. McLoughlin Blvd, Vancouver, WA 98661; (206) 695-1334.

CALIFORNIA. BE/BC Internist to join staff of eight Internists in 14 physician multispecialty group located in central San Joaquin Valley. Competitive starting salary and full benefits. Excellent living and practice environment. Send CV to Frank Kelley, MD, Kaweah Medical Group, 222 W. Willow, Visalia, CA 93291.

UROLOGIST BC/BE. To be second Urologist in a 35 physician multispecialty clinic. Guaranteed salary and immediate full participation in incentive program. Excellent benefit package and excellent recreational, cultural, and educational opportunities. Send CV to Search Committee, 55 W. Tietan, Walla Walla, WA 99362.

OREGON. INTERNIST BC/BE needed in busy four person group in dry part of state, town 14,000. Great place to live and work. CV to N. Sitz, MD, 1100 Southgate, Suite #2, Pendleton, OR 97801; (503) 276-1911.

FAMILY PRACTICE/GENERAL PRACTICE wanted for full-time practice to work three days a week and share with another Practitioner. Rural setting, good pay, nice people. Can commute for two nights a week, one hour Sacramento, one hour and 15 minutes Nevada City, two hours San Francisco. Contact Charles Rath, MD, 199 E. Webster St, Colusa, CA 95932; (916) 458-7739.

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P.O. Box 8241
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(Continued on Page 610)

CONTINUING MEDICAL EDUCATION

(Continued from Page 606)

May 18-21—**Health Life Planning** (Sponsor: UUMC). Wed-Sat. 32 hrs. Park City Prospector Square. Contact: (801) 521-4625.

June 9-11—**Castle Country Medical Symposium** (Sponsor: CH). Thurs-Sat. 14 hrs. Raddison Hotel, Price. Contact: (801) 637-4800.

June 11-13—**Health Life Planning** (Sponsor: UUMC). Sat-Mon. 32 hrs. Salt Lake City Raddison. Contact: (801) 521-4625.

August 13-15—**Retrieved Implants and Biomaterials** (Sponsor: UUMC). Fri-Sun. Contact: Rosalie Lammle, (801) 581-8664.

September 22-24—**Central Association of Obstetricians & Gynecologists** (Sponsor: UUMC). Thurs-Sat. 10.5 hrs. Salt Lake City Marriott. Contact: (801) 333-0988.

SPONSORS OF COURSES—ABBREVIATIONS

AHA: American Heart Association, Utah Affiliate, 645 E 400 South, Salt Lake City 84102. (801) 322-5601.

BYUHS: Brigham Young University Health Services, McDonald Student Health Center, Brigham Young University, Provo 84602. (801) 378-2771.

CH: Castleview Hospital (formerly Carbon Hospital), RFD 2, Box 46, Price 84501. (801) 637-4800.

CWH: Cottonwood Hospital, 5770 S 300 East, Salt Lake City 84101. (801) 262-3461.

DMC: Dixie Medical Center, 544 S 400 East, St George 84770. (801) 673-9681.

HCH: Holy Cross Hospital, 1045 E First South, Salt Lake City 84102. (801) 350-4744.

ITS: Intermountain Thoracic Society, 1616 S 11th East, Salt Lake City 84105. (801) 484-4456.

LDSH: LDS Hospital, 8th Ave and "C" St, Salt Lake City 84143. (801) 321-1100.

LRH: Logan Regional Hospital, 1400 N 5th East, Logan 84321. (801) 752-2050.

MDH: McKay-Dee Hospital Center, 3939 Harrison Blvd, Ogden 84409. (801) 399-4141.

MVH: Mountain View Hospital, 1000 E Highway 6, Payson 84651. (801) 465-9201.

144: 144th Evacuation Hospital, PO Box 8000, Salt Lake City 84108. (801) 524-3924.

OSS: Ogden Surgical Society, PO Box 9311, Ogden 84409.

PCMC: Primary Children's Medical Center, 320 12th Ave, Salt Lake City 84103. (801) 363-1221.

PVH: Pioneer Valley Hospital, 3460 S 4155 West, West Valley City 84120. (801) 968-9061.

SMH: St Mark's Hospital, 1200 E 3900 South, Salt Lake City 84117. (801) 268-7111.

UOS: Utah Ophthalmological Society, 540 E 500 South, Salt Lake City 84102. (801) 355-7477.

USH: Utah State Hospital, PO Box 270, Provo 84603-0270. (801) 373-4400.

UUMC: University of Utah Medical Center, 50 N Medical Dr, Salt Lake City 84132. (801) 581-2258.

UVRMC: Utah Valley Regional Medical Center, 1034 N Fifth West, Provo 84604. (801) 373-7850.

VAMC: Veterans Administration Medical Center, 500 Foothill Dr, Salt Lake City 84148. (801) 582-1565.

VVMC: Valley View Medical Center, 595 S 75 East, Cedar City 84720. (801) 586-6587.

WASHINGTON

This listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. To list Category 1 programs here please send information at least two months in advance to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 900, Seattle, WA 98121; or phone (206) 441-WSMA.

Brochures and registration forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

May 19-20—**Update on Travel and International Medicine.** Seattle. Thurs-Fri. Contact: Maria Lilja, (206) 543-1050.

May 19-21—**Emergency Medicine Update.** Seattle. Thurs-Sat. Contact: VMMC.

(Continued on Page 611)

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GASTROENTEROLOGIST position available with multispecialty group; BE/BC required; strong incentive plan; benefits included; retirement program and located in San Luis Obispo, California on the central coast. Send CV to Administration/Recruitment, San Luis Medical Clinic, 1235 Osos St, San Luis Obispo, CA 93401.

FAMILY PRACTITIONER position available with multispecialty group; BE/BC required; strong incentive plan; benefits included; retirement program and located in San Luis Obispo, California on the central coast. Send CV to Administration/Recruitment, San Luis Medical Clinic, 1235 Osos St, San Luis Obispo, CA 93401.

GENERAL INTERNIST position available with multispecialty group; BE/BC required; strong incentive plan; benefits included; retirement program and located in San Luis Obispo, California on the central coast. Send CV to Administration/Recruitment, San Luis Medical Clinic, 1235 Osos St, San Luis Obispo, CA 93401.

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Sandy Ward, Administrator
497 W Lott
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or call (307) 684-5521

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For more information:

Send CV or contact Patty House
Health Resource Services Group
1200 5th Ave, Suite 2000
Seattle, WA 98111
(206) 223-6351.

30 MEMBER MULTISPECIALTY, San Francisco bay area private practice group seeks second Orthopaedist to join existing one, starting July 1988. Must be BE/BC. Incentive based income. Submit CV to Michael E. Sondel, CEO, Family Doctor Medical Group, 1617 Broadway, Vallejo, CA 94589-2495; (707) 553-6023.

OCCUPATIONAL/FAMILY PRACTICE. Excellent opportunities with west coast's leading provider of Occupational/Family Practice medicine. Full/part-time positions throughout California and Washington (Seattle/Tacoma). Current license/CPR. Prior outpatient/family practice/industrial-type trauma experience. Attractive salary/incentives/benefits/malpractice. Contact Personnel Director, ReadiCare, Inc, 446 Oakmead Pkwy, Sunnyvale, CA 94086; (800) 237-3234. Join our dynamic team of professionals. Practice and live in an incomparable environment.

PEDIATRICIAN—SUNNY SOUTHERN CALIFORNIA. Rapidly growing, family oriented community at the foot of the mountains near Palm Springs needs another Pediatrician. Beautiful hospital expanding its services will provide financial guarantee for the right BE/BC physician. For more information and a personal interview, please call Jeffrey Gowan at (800) 288-1210 and/or send your CV to Merritt, Hawkins & Associates, 500 N. Newport Blvd, Ste 204, Newport Beach, CA 92663.

FAMILY PRACTITIONER. BE/BC Family Practitioner with knowledge of Spanish to become shareholder and partner with 20 plus MD multispecialty group. Training important. Guarantee salary, malpractice insurance, health insurance, plus. Send CV to Number 98, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

INTERNIST NEEDED FULL-TIME. Primary Care position for Board certified Internist is now available with a growing San Francisco Health Plan. The position includes both inpatient and outpatient responsibilities. Send CV to Medical Director, French Health Plan, 4131 Geary Blvd, San Francisco, CA 94118.

(Continued on Page 614)

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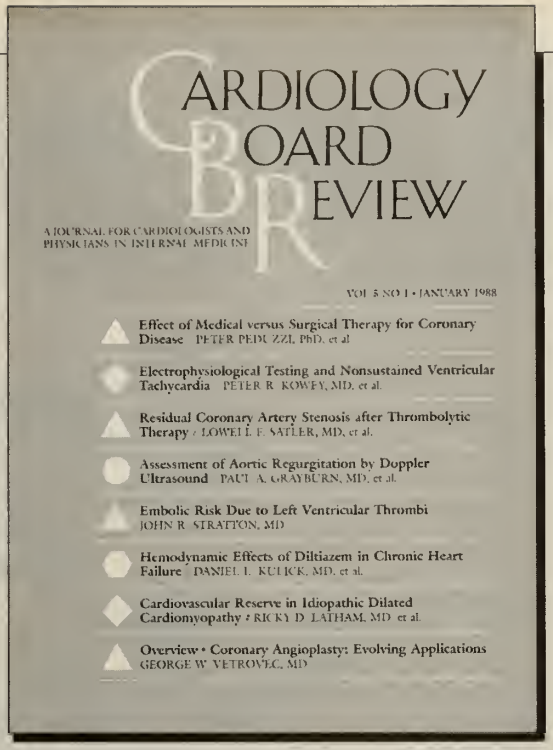
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*Journals reviewed include: *Circulation, American Heart Journal, Journal of the American College of Cardiology, British Heart Journal, Chest, The American Journal of Cardiology, The New England Journal of Medicine, Annals of Internal Medicine, American Journal of Medicine*, and *The Journal of the American Medical Association*.

CONTINUING MEDICAL EDUCATION

(Continued from Page 609)

May 26-27—**Alzheimer's Disease.** Seattle. Thurs-Fri. Contact: U/W, Maria Lilja, (206) 543-1050.

June 3—**Topics in General Internal Medicine.** Seattle. Fri. Contact: VMMC.

June 9—**Health Care and Anti-Trust.** Seattle. Thurs. Contact: U/W, Maria Lilja, (206) 543-1050.

June 9-10—**Update in Clinical Neurology.** Seattle. Thurs-Fri. Contact: Northwest Hospital, (206) 364-0500, Ext 1621.

June 9-11—**Obstetric Ultrasound.** Seattle. Thurs-Sat. Contact: Robin Murray, (202) 863-2543.

June 17-18—**Renal Disorders: Medical and Surgical Aspects.** Seattle. Fri-Sat. Contact: U/W, Maria Lilja, (206) 543-1050.

June 20-24—**Pathology of Lung Cancer.** Seattle. Mon-Fri. Contact: VMMC.

July 22-24—**First International Symposium on Pediatric Pain.** Seattle. Fri-Sun. Contact: U/W, Maria Lilja, (206) 543-1050.

July 29-31—**Seafair Anesthesia X.** Seattle. Fri-Sun. Contact: VMMC.

COURSE SPONSORS AND CONTACT INFORMATION

CME HARBORVIEW—Contact: Gayle Splater, Cytology Continuing Education, Dept. of Pathology, Harborview Medical Center, 325 Ninth Avenue, Seattle, WA 98104. (206) 223-5953.

CME PIERCE COUNTY—Contact: Mrs Maxine Bailey, Executive Director, College of Medical Education, 705 South Ninth, No. 203, Tacoma, WA 98405. (206) 627-7137.

U/W (UNIVERSITY OF WASHINGTON)—Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

WSMA—Washington State Medical Association, Continuing Medical Education, 2033 Sixth Ave, Suite 900, Seattle, WA 98121. (206) 441-9762.

VMMC (VIRGINIA MASON MEDICAL CENTER)—Contact: Linda Orgel, Division of Continuing Medical Education, Virginia Mason Medical Center, PO Box 900, Seattle, WA 98111. (206) 223-6898.

August 1-5—**Postgraduate Seminar in Psychology: Modern Approaches to Psychological Interviewing.** Ellensburg. Mon-Fri. Contact: Central Washington University, (509) 963-2381.

August 5—**Otology Update.** Seattle. Fri. Contact: VMMC.

August 8-14—**Summer Seminar in Medical Ethics and History.** Seattle. Mon-Sun. Contact: U/W, Maria Lilja, (206) 543-1050.

August 11-12—**Surviving the Elements.** Seattle. Thurs-Fri. Contact: U/W, Maria Lilja, (206) 543-1050.

August 29—**NW Regional Perinatal Conference: Current Issues in OB/GYN, Neonatology and Pediatrics.** Coeur d'Alene, Idaho. Thurs. Contact: (509) 624-3182.

August 31-September 3—**Second International Forum of Otorhinolaryngology.** Seattle. Wed-Sat. Contact: U/W, Maria Lilja, (206) 543-1050.

September 17-24—**Effective Management of Common Sports Injuries.** San Juan Islands. Sat-Sat. Contact: Kathy Rairigh, EPIC Expeditions, (208) 788-4995.

September 22-24—**Orthopedic Biomechanics.** Seattle. Thurs-Sat. Contact: VMMC.

WYOMING

June 23-26—**Wyoming Medical Society Annual Meeting.** Jackson Lake Lodge, Moran. Thurs-Sun. Contact: WMS, PO Drawer 4009, Cheyenne 82003-4009. (307) 635-2424.

July 18-22—**6th Annual Update in Clinical Microbiology and Immunology.** University of Utah Medical Center at Jackson Hole. Mon-Fri. 25 hrs. Contact: UUMC, 50 N Medical Dr, Salt Lake City, UT 84132. (801) 581-2258. ◆

THE ARIZONA MEDICAL ASSOCIATION, INC.

ANNUAL MEETING AND SCIENTIFIC PROGRAM SCHEDULE

JUNE 9 — 11, 1988 • LOEWS VENTANA CANYON RESORT • TUCSON, ARIZONA

SCHEDULE OF EVENTS

Thursday, June 9, 1988

Current Perspectives Programs

8:00 AM – 12 Noon	Legal/Ethical	Salons J & K
	Infectious Diseases	Salons H & I
	Nuclear	Salon L

Current Perspectives Programs

1:00 PM – 5:00 PM	Musculoskeletal Disorders	Salons J & K
	Pharmacotherapeutics	Salons H & I
	Nuclear	Salon L
1:00 PM – 5:00 PM	Hospital Medical Staff Section Program and Annual Meeting	Coronado
1:00 PM – 5:00 PM	Arizona Chapter, American College of OB/GYN	Pavilion A
7:00 PM	"An Evening with Mark and Marv" Reception and Steak Fry	BBQ Area

Friday, June 10, 1988

6:00 AM – 8:00 AM	Executive Committee Breakfast	Executive Boardroom
8:00 AM – 10:00 AM	Board of Directors' Meeting	Salon D
10:00 AM – 12 Noon	House of Delegates	Salon B
12 Noon – 4:00 PM	Past Presidents' Luncheon	Saguaro
2:00 PM – 5:00 PM	Amendments Reference Committee	Salon D
2:00 PM – 5:00 PM	Resolutions Reference Committee	Salon K
7:00 PM	President's Reception	Foyer
8:00 PM	President's Banquet	Salons B & C

Saturday, June 11, 1988

6:30 AM – 8:00 AM	Maricopa County Caucus	Rincon
6:30 AM – 8:00 AM	Pima County Caucus	Coronado
8:00 AM – 12 Noon	House of Delegates	Salon B
12 Noon – 3:00 PM	Board of Directors' Luncheon	Coronado

For further information or registration material, please contact the Arizona Medical Association, (602) 246-8901.

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(Continued from Page 610)

PHYSICIAN WANTED

Physicians wanted for leading clinic

Prestigious Chicago-based clinic group specializing in the treatment of venous disorders is expanding nationally. Our newest clinics in Los Angeles, San Francisco, Seattle, San Diego and Phoenix are in need of physicians trained in internal medicine—or who have a broad base of medical experience. We will provide complete training in the latest proprietary techniques of treating venous disorders. We offer a six figure salary and bonus potential, along with malpractice insurance and health benefits. And since there are no weekend hours and a 40-hour work week, you will have plenty of leisure time. You won't have to worry about soliciting for patients or fighting insurance companies.

This is an outstanding opportunity for professional and financial advancement. If you are motivated to build a rewarding practice with the leader in the treatment of venous disorders, send your resume to:

Medical Director

Vein Clinics of America

2340 S. Arlington Heights Road
Arlington Heights, Illinois 60005

30 MEMBER MULTISPECIALTY, San Francisco bay area private practice group seeks Pediatrician starting July 1988. Must be BE/BC. Incentive based income. Submit CV to Michael E. Sondel, CEO, Family Doctor Medical Group, 1617 Broadway, Vallejo, CA 94589-2495; (707) 553-6023.

THE TOWN OF TRINIDAD, COLORADO is currently looking for a Family Practitioner/General Practitioner and Internal Medicine Specialist for private practice openings. Trinidad is located approximately 80 miles south of Pueblo, Colorado on the Front Range of the Rocky Mountains. The area enjoys an excellent climate with a great deal of recreational activities. Also, skiing is available within 45 minutes at Cuchara Valley Ski Area. Interested individuals should contact Ron Shafer, Administrator, Mount San Rafael Hospital, 410 Benedicta Ave, Trinidad, CO 81082; (719) 846-9213.

OUTSTANDING OPPORTUNITY. General Internist, BE/BC, and Oncologist with Internal Medicine strength. Private practice or affiliation available, San Francisco north bay area community. Send résumé to Number 84, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

PHYSICIANS WANTED

SAN DIEGO STATE UNIVERSITY
Student Health Services—Physician II

Ten month position. BC required. Family Practice strongly preferred. Salary range $5,488 to $6,642 per month. Send letter of interest and CV to Ralph Hernandez, MD, Chief of Clinical Services, Student Health Services, San Diego State University, San Diego, CA 92182.

ORTHOPEDIST. The west coast's leading Occupational/Family Practice medical provider has full-time/part-time opportunities for Orthopedic Specialists in California and Washington (Seattle/Tacoma). Attractive package includes guaranteed salary, incentive bonus, and benefits. Current license. Contact Personnel Director, ReadiCare, Inc, 446 Oakmead Pkwy, Sunnyvale, CA 94086; (800) 237-3234. Join our dynamic team of professionals. Practice and live in an incomparable environment.

30 MEMBER MULTISPECIALTY, San Francisco bay area private practice group seeks non-invasive Cardiologist starting July 1988. Must be BE/BC. Incentive based income. Submit CV to Michael E. Sondel, CEO, Family Doctor Medical Group, 1617 Broadway, Vallejo, CA 94589-2495; (707) 553-6023.

PEDIATRICIAN. BE/BC Pediatrician with knowledge of Spanish to become shareholder and partner with 20 plus MD multispecialty group. Training important. Guarantee salary, malpractice insurance, health insurance, plus. Send CV to Number 99, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

INTERNIST, BC/BE, to join two member primary care clinic, suburb, Seattle, Washington. Spacious, new office near top rate hospital. Send letter of career goals, interests, and CV to Number 100, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

ACADEMIC EMERGENCY PHYSICIAN. Unique position combining half-time academic attending at University of Washington, University Hospital Emergency Department and half-time Medical Advisor to King County Paramedic Program. Responsibilities as attending include supervision of housestaff and medical students, clinical care, and teaching. Responsibilities as Medical Advisor include assisting the manager of the King County Emergency Medical Services Division, working with local paramedic medical directors to ensure consistency and coordination in the provision of services, develop and assist in EMS training programs and continuing education, assist in evaluation research of new or existing medical treatments, and represent the Division with the local medical community and professional regulatory agencies. Qualifications include BE/BC Internal Medicine, experience in Emergency Medicine and emergency medical services. Appointment is in the Department of Medicine, University of Washington. Rank and salary dependent upon qualifications. Female and minority candidates are encouraged to apply. Send letter of interest and CV to Mickey Eisenberg, MD, PhD, Emergency Medicine Service, University Hospital, RC-02, 1959 NE Pacific St, Seattle, WA 98195.

30 MEMBER MULTISPECIALTY, San Francisco bay area private practice group seeks Pediatrician or Family Practice Physician for urgent or episodic primary care outpatient clinic. Full-time. Must be BE/BC. Incentive based income. Submit CV to Michael E. Sondel, CEO, Family Doctor Medical Group, 1617 Broadway, Vallejo, CA 94589-2495; (707) 553-6023.

INVASIVE CARDIOLOGIST. Aggressive catheterizing BC/BE Cardiologist wanted for expansion of practice in California's central valley. Base salary and incentives depending on experience with potential for early partnership. Please respond with CV to Box 3211, Modesto, CA 95353

PHYSICIANS WANTED

SOUTHERN CALIFORNIA

Enjoy professional challenge and growth with a successful and expanding HMO in Southern California. CIGNA Healthplans of California is seeking Specialists and Primary Care Physicians committed to concepts of prevention and health maintenance to join our facilities in Los Angeles and Orange Counties. We offer an excellent compensation and benefits package including profit sharing. For consideration, please forward CV to:

Director/Physician Recruitment
CIGNA Healthplans of California
505 N. Brand Blvd, Suite 400-49
Glendale, CA 91203

OPENINGS for one or two General and one Vascular Surgeon in 175 physician, multispecialty group. Offices adjacent to modern 230-bed hospital in suburbs of south San Jose near excellent recreational facilities. Competitive salary, generous fringe benefits including paid educational leave, vacation, insurance, and retirement. Contact Latimer H. Booth, MD, Chief, Department of Surgery, The Permanente Medical Group, Inc, 260 International Cir, San Jose, CA 95119.

SEVERAL OPENINGS AVAILABLE for Family Practitioners throughout western and central North Dakota. This large multispecialty group is seeking physicians for several satellites. All positions include a lucrative salary guarantee, full benefit package, and coverage. For more information, contact Durham Medical Search, Inc, 6300 Transit Rd, PO Box 478, Depew, NY 14043; or call 1 (800) 633-7724.

EUGENE, OREGON. Well-established, eight physician Family Practice group is seeking BC/BE Family Physician with interest in OB. Anticipate partnership after one year. Exceptional cultural and recreational opportunities. Home of the University of Oregon. Please send CV to Rob Daugherty, MD, River Road Medical Group, 2400 River Rd, Eugene, OR 97404; or call (503) 688-7527.

OB/GYN—SUNNY SOUTHERN CALIFORNIA. Rapidly growing, family oriented community at the foot of the mountains near Palm Springs needs another OB/GYN. Beautiful hospital expanding its services will provide financial guarantee for the right BE/BC physician. For more information and a personal interview, please call Jeffrey Gowan at (800) 288-1210 and/or send your CV to Merritt, Hawkins & Associates, 500 N. Newport Blvd, Ste 204, Newport Beach, CA 92663.

WASHINGTON. Full-time Emergency Physician needed for moderate volume ED in Yakima area. $100,000 possible plus partial malpractice coverage. Near mountains, skiing, etc. Two and one-half hours from Seattle. Send CV to Ted Palmatier, MD, FACEP, 110 S. Ninth Ave, Yakima, WA 98902; or call (509) 575-5060.

FAMILY PRACTICE PHYSICIAN. Full-time in a busy walk-in medical clinic. Located in Visalia, California (Tulare County). Malpractice insurance, salary and ECT. Please call (209) 627-5555 for more information.

GENERAL SURGEON. Opportunity for BC/BE Surgeon with fellowship or experience in Vascular Surgery to join Surgeon in active practice in southeastern Washington state; well-equipped 71-bed hospital undergoing expansion. Send current CV to J. Griffith, PO Box 6128, Kennewick, WA 99336.

CALIFORNIA

Primary Care Physicians needed to work as *locum tenens* in northern California. Radiologists needed statewide. High salary, paid malpractice. Work whenever you like. Permanent placements as well.

Contact Carol Sweig, Director, (415) 673-7676. Western Physicians Registry, 710 Van Ness Ave, San Francisco, CA 94102.

PHYSICIANS WANTED

FAMILY PRACTICE

Excellent opportunity for Family Physician to replace one associate who is retiring. Established Family Practice in Norwalk, California, will guarantee basic salary plus percentage. Partnership a possibility.

(213) 868-7706

INTERNAL MEDICINE. A BC/BE Internist with/without subspecialty needed to join busy practice of two BC Internists in growing town on beautiful coast of northern California. Outdoor activities unlimited, great setting for family life. New state employer. Practice half hospital-based (new facility in two years) with full range ICU procedures and half office-based. Frequent consultations. Salary guarantee, benefits package, profit sharing, early partnership potential. Call or write John H. Jackson, MD, 200 A St, Ste B, Crescent City, CA 95531; (707) 464-8331.

PHYSICIAN OPENING. Ambulatory care/minor emergency center. Full/part-time for Family Practice/Internal Medicine/Emergency Medicine trained, experienced physician located in Tacoma area. Flexible scheduling, pleasant setting, quality medicine. Contact David R. Kennel, MD, 5900 100th St Southwest, Ste 31, Tacoma, WA 98499; (206) 584-3023 or 582-2542.

ONCOLOGIST/INTERNIST BC/BE wanted to join hospital-based multispecialty clinic near San Francisco. Complete benefit package. Send résumé to Gary Hillman, MD, Chief, Department of Medicine, Permanente Medical Group, 1150 Veterans Blvd, Redwood City, CA 94063; or call (415) 780-2626.

FAMILY PRACTICE—SUNNY SOUTHERN CALIFORNIA. Rapidly growing, family oriented community at the foot of the mountains near Palm Springs needs another Family Practitioner. Beautiful hospital expanding its services will provide financial guarantee for the right BE/BC physician. For more information and a personal interview, please call Jeffrey Gowan at (800) 288-1210 and/or send your CV to Merritt, Hawkins & Associates, 500 N. Newport Blvd, Ste 204, Newport Beach, CA 92663.

INTERNIST. We are seeking a BC/BE Internist with a special interest in Cardiology to join a university-affiliated, hospital and clinic-based, primary patient care group. Clinical skills in an ICU/CCU setting are important, as well as the ability to interact with an 18 member Family Practice Residency Program. Send CV to John Schatz, MD, Chief, Department of Cardiology, Natividad Medical Center, 1330 Natividad Rd, Salinas, CA 93906.

WASHINGTON. Excellent opportunity for caring BC/BE physician to join a 35 member multispecialty clinic as the second physician in our expanding facility based Immediate Care Department. Competitive salary and generous fringe benefits including paid education leave, vacation, insurance, and retirement. Send inquiries and CV to R. G. Caudill, MD, Walla Walla Clinic, 55 W. Tietan, Walla Walla, WA 99362.

OB/GYN—IDAHO-SUN VALLEY. Skiing is one of the benefits of having your practice in this recreation-rich area. Hospital is expanding its OB/GYN services and needs one to two BE/BC hardworking OB/GYNs to service this area. Big practice. Support of excellent, quality medical staff. For more information call Jeffrey Gowan at (800) 288-1210 and/or send CV to 500 N. Newport Blvd, Ste 204, Newport Beach, CA 92663.

MEDICAL DIRECTOR/FAMILY PHYSICIAN, San Francisco bay area. Community clinic needs part-time Medical Director, flexible hours, with clinical and administrative duties. Competitive pay, malpractice provided. Contact Lisa Jafferies, 2470 Alvin Ave, #3, San Jose, CA 95121; (408) 274-8400. Start date—summer.

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PHYSICIANS WANTED

Western States OPENINGS

Many multispecialty groups and hospitals have asked us to recruit for over 300 positions of various specialties. Both permanent and locum tenens. Send CV to:
Western States Physician Services,
407 S. Clovis Ave, Ste 108, Fresno, CA 93727.
Or call (209) 252-3000.

INTERNIST, BC/BE, California license. Women's care clinic. Duties will include admissions and in-patient care. Send résumé to Dr Susann J. Steinberg, Medical Director, Access Health Care, 26 California St, San Francisco, CA 94111.

PHYSICIAN part-time for Internal Medicine practice in the East Bay. Residency training in Internal Medicine preferred. Malpractice insurance paid. Possible association in future. Call (415) 223-7901, or send CV to 4450 San Pablo Dam Rd, El Sobrante, CA 94803.

FAMILY PRACTICE—IDAHO-SUN VALLEY. Skiing is one of the great amenities of living and practicing in this recreation-rich area. If you desire to practice in association with other young BC Family Practitioners who do OB in a nice family-oriented community and are supportive of another new physician, if you wish to make an above-average living, if you would like to have an option of practice management provided for you, please call Jeffrey Gowan at (800) 288-1210 and/or send CV to 500 N. Newport Blvd, Ste 204, Newport Beach, CA 92663 for additional details and a personal interview.

SURGICAL ONCOLOGIST OR GENERAL SURGEON. Outstanding opportunity for a well-trained Surgical Oncologist or General Surgeon to affiliate as an Associate with a premier northern California surgical practice located in the north Sacramento area. Generous salary and benefits. Partnership offered two to five years. A turn-key situation located in a beautiful growing community. Call collect Physician Relations Manager, (916) 537-5009.

BEAUTIFUL MONTEREY BAY. Immediate opportunity for a friendly, skilled, Family Practice or Emergency Physician to join highly respected urgent care group with two beautiful Santa Cruz clinics. Committed to high quality care. Nice people, flexible scheduling, comprehensive benefits, including: paid malpractice, group health insurance, long-term disability insurance, no nights, rapid advancement to full partnership in an outstanding place to live. Please send CV to Robert Korns, MD, 6800 Soquel Dr, Aptos, CA 95003 or call (408) 662-3611.

PHYSICIANS WANTED

PHYSICIANS WANTED. We have full and part-time locum tenens opportunities available with guaranteed incomes and paid malpractice. For more information, contact John Smith, Locum Tenens, Inc (A Division of Jackson and Coker), 400 Perimeter Center Terrace, Ste 760 WJM, Atlanta, GA 30346; 1 (800) 544-1987.

GENERAL INTERNIST needed for large hospital-based multispecialty clinic. University associated residency program. Attractive salary and complete benefit package. Pleasant setting. BC/BE. California license required. Contact Dennis L. Ostrem, MD, Chief Internal Medicine, The Permanente Medical Group, Inc, PO Box 254999, Sacramento, CA 95865-4999 or call (916) 973-5781. An Equal Opportunity Employer.

ASSOCIATE—ORTHOPAEDIC SURGEON. BC/BE Orthopaedist with California license wanted to join busy solo Practitioner. Surburban practice in rapidly growing community, Sacramento County. Very desirable area to live and raise family. Excellent opportunity for rapid growth of quality practice. Send CV to Gabriel S. Salzman, MD, PO Box 1046, Folsom, CA 95630.

FAMILY PRACTITIONER or GENERAL PRACTITIONER—BC/BE. For Family Practice in a large central California community and migrant health clinic located in the central San Joaquin Valley serving large Hispanic and Southeast Asian medically underserved population. Competitive salary with excellent fringe benefits and paid malpractice. Send CV and inquiries to Director, Sequoia Community Health Foundation, Inc, 2790 S. Elm Ave, Fresno, CA 93706.

OB/GYN, SEATTLE AREA. Rapidly growing practice seeks third OB/GYN. Come practice in a picturesque community on Puget Sound. Nearby mountains and lakes provide limitless recreational opportunities. University of Washington continuing education minutes away. For excellent incentive-oriented compensation and benefits contact Philip DuBois, MD, 7935 216th St SW, Ste E, Edmonds, WA 98020; (206) 775-0681.

PEDIATRICIAN, BE/BC, needed July 1988 in four-season playground. Excellent practice opportunity with positive financial success. Send CV to Dr Gerald E. Carlson, Women's Medical Clinic, 1203 10th St South, Nampa, ID 83651; (208) 467-2400.

FAMILY PRACTITIONER—BC/BE. For rural health clinic at the foot of Sequoia National Park. Send salary history and CV to Personnel, Woodlake Family Health Center, 180 E. Antelope, Woodlake, CA 93286. E.O.E.

(Continued on Page 617)

SURGEONS AND INTERNISTS:

THE ARMY NEEDS PHYSICIANS PART-TIME.

The Army Reserve offers you an excellent opportunity to serve your country as a physician and a commissioned officer in the Army Reserve Medical Corps. Your time commitment is flexible, so it can fit into your busy schedule. You will work on medical projects right in your community. In return, you will complement your career by working and consulting with top physicians during monthly Reserve meetings and medical conferences. You will enjoy the benefits of officer status, including a non-contributory retirement annuity when you retire from the Army Reserve, as well as funded continuing medical education programs. A small investment of your time is all it takes to make a valuable medical contribution to your community and country. For more information,

CONTACT YOUR AMEDD PERSONNEL COUNSELOR LISTED BELOW:

CALL COLLECT:

California and Hawaii — Major Shackleton (415) 751-1616

Alaska, Oregon, Idaho and Washington — Major Lawhon (206) 967-2524

Arizona, Nevada and Utah — Major McCullough (602) 279-4581

Colorado, Montana, N. Dakota, S. Dakota and Wyoming — Captain North (303) 361-8841

ARMY RESERVE. BE ALL YOU CAN BE.

(Continued from Page 615)

PHYSICIANS WANTED

PHYSICIAN WANTED. Family Practice Physician to join 16 physician multispecialty group with attached 40-bed hospital located in southern Idaho. Contact Business Administrator, Box 1233, Twin Falls, ID 83301.

INTERNISTS, OB/GYN, PEDIATRICIAN, ORTHOPEDIC SURGEONS and NEUROSURGEONS for private practice situations in Washington, Nevada, California, Louisiana, Florida, Texas. Most situations are with established physicians although some are hospital sponsored. For additional information, please contact Eloise Gusman, 1 (800) 535-7698 or (504) 893-4879 or send CV to PO Box 1685, Covington, LA 70434-1685.

MONTEREY PENINSULA, CALIFORNIA. BC/BE General Internist to join four other Internists now in multispecialty group. Guaranteed income arrangement leading to partnership. Busy, well established clinic practice. Excellent office, lab, x-ray equipment. Outstanding community hospital. Submit CV, availability date to Robert H. Cleland, MD, Central Medical Group, 505 Central Ave, Pacific Grove, CA 93950.

LONG ESTABLISHED, MULTISPECIALTY GROUP PRACTICE on northern California coast is seeking a Family Practitioner, BC/BE. Immediate salaried position leading to partnership status within one year. Please direct CV to Connie K. Kellough, Administrator, Medical Group of Watsonville, 850 Freedom Blvd, Watsonville, CA 95076.

ENJOY COUNTRY LIVING and outstanding year 'round outdoor recreation, excellent school system, clean environment! Join two BC Internists with growing practice in historical Wyoming community. We seek BE/BC Internist candidates recently trained or in university affiliated program. Income guarantee, paid malpractice and health insurance, more! Contact Cynthia Lacro, PROSEARCH, 305 NE 102nd Ave, Portland, OR 97220; 1 (800) 237-6906.

PHYSICIANS WANTED

OCCUPATIONAL MEDICINE PHYSICIAN. Excellent opportunity for experienced BC/BE Occupational Medicine Physician. Prefer candidates with boards in Internal Medicine to join large multispecialty group. Administrative skills highly desirable for self-motivated individual with wide range of practice opportunities. Excellent salary and benefits are offered. Located in central San Diego. Send CV to Linda Lyons, MD, Medical Director, Scripps Clinic San Diego, 2020 Genesee Ave, San Diego, CA 92123.

FAMILY PRACTITIONER, people oriented and with urgent care experience for private general practice in desirable S.F. bay area location. See average of 30 patients per 12 hour shift in exceptionally pleasant and well-equipped work environment. No hospital or on-call obligations. Family Practice residency or equivalent experience and long-term interest are essential. Will consider full- and part-time candidates. Do not call, but send CV to David Wetterholt, MD, Saratoga Walk-in Clinic, 12224 Saratoga-Sunnyvale Rd, Saratoga, CA 95070.

INTERNIST—SUNNY SOUTHERN CALIFORNIA. Rapidly growing, family oriented community at the foot of the mountains near Palm Springs needs another Internist. Beautiful hospital expanding its services will provide financial guarantee for the right BE/BC physician. For more information and a personal interview, please call Jeffrey Gowan at (800) 288-1210 and/or send your CV to Merritt, Hawkins & Associates, 500 N. Newport Blvd, Ste 204, Newport Beach, CA 92663.

FAMILY PRACTITIONER. Busy four physician Family Practice group (including OB) seeks replacement for partner departing fall, 1988. Located in Alaska's capital city in the Tongass National Forest offering year 'round recreation including skiing, boating, and hiking. Guaranteed salary with excellent fringe benefits and opportunity for partnership within one year. Send CV to Sarah A. Isto, MD, Valley Medical Care, Inc, 9309 Glacier Hwy, B-301, Juneau, AK 99801; (907) 789-3181.

SITUATION WANTED

ADMINISTRATION/MANAGEMENT for Health Care Practices; HMO; other related services. Health professional with multi backgrounds and experience in Health Care, now a law student. If have position—contact Dr Robert L. Burns, 2351 Bonita, Highland, CA 92346; (714) 864-7141 for résumé.

INTERNIST, ENDOCRINOLOGIST. BE, trained at UCSF, prior outpatient primary care experience, desires position consisting of specialty and general Internal Medicine. Reply to Number 97, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

MEDICAL PRACTICE OPPORTUNITIES

RETIRING DOCTOR

Selling excellent Family Practice; best building; choice location in town. Glorious northern California area, two hours to San Francisco, one hour to Lake Tahoe. Gross $260,000. Also . . . CALIFORNIA/NATIONWIDE: IM, Ped, Pulm, Cardio, Ortho, Surg, FP, Derm, Psych, OB/GYN, Oph, Oto, Urol, Anesthesiology **BRADSHAW ASSOCIATES, Practice Sales/Recruitment/Valuations, 21 Altamount Dr, Orinda, CA 94563; (415) 376-0762.**

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(Continued on Page 618)

MEDICAL PROGRAM DIRECTOR

Correctional Medical Services (SANTA ANA-ORANGE COUNTY)

Seeking a Medical Program Director to oversee the expanding medical component of the Correctional Medical Services program. The incumbent will report to the Program Administrator and will oversee a medical care delivery system, provide medical consultation services for medical and/or ancillary staff, supervise other Physicians and Nurse Practitioners, develop medical protocol and represent Correctional Medical Services as a liaison with other County agencies/departments and local health care providers, including the University of California Irvine Medical Center. Must be a California licensed Physician with five years of increasingly responsible medical and administrative experience. SALARY $57,216 to $86,400 ANNUALLY. The starting salary is negotiable. Excellent fringe benefit package. **Send curriculum vitae to Rosie Rivera, Health Care Agency Personnel, 515 N. Sycamore, Santa Ana, CA 92701 or call (714) 834-6851.** Affirmative Action Employer M/F.

(Continued from Page 617)

PRACTICES AVAILABLE

BUY AN ARIZONA PRACTICE. We're the medical practice specialist of Arizona. FREE registration. Contact T. Ross, MD, Practice Opportunities, Realty Executives, 6520 N. Scottsdale Rd, M-110, Scottsdale, AZ 85253; (602) 991-4273.

BEAUTIFUL PUGET SOUND FAMILY PRACTICE available. Complete office, lab and x-ray equipment. Practice gross over 225K. Price $35,000. Reply to Number 74, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

FAMILY PRACTICES IN SAN DIEGO COUNTY. Long established—doctors retiring. Various prices with low down payments. Other specialty practices available, C.B.I. (619) 283-7009.

NAPA INTERNAL MEDICAL PRACTICE. Long established and highly regarded practice being made available by retiring physician. 1987's collections were $160,000 plus with available profits of $80,000 plus. Energetic physician will develop potential. Full price $40,000. Contact Professional Practice Sales and request detailed prospectus. (415) 665-8500.

PRACTICE AND/OR CLINIC BUILDING FOR SALE. Dermatologist retiring; active practice; good location in Bellingham, Washington. Clinic layout works for several specialties. Seller contract. Call David at The Friedrich Group, (206) 842-5248, or Bill at Equity Investments, Inc, (206) 671-0600. Bellingham is home to Western Washington University. Recreational opportunities available at San Juan Islands, Puget Sound, and Cascade Mountains. One hour to Vancouver, BC; 90 minutes to Seattle.

SOLO FAMILY PRACTICE FOR SALE OR LEASE. One and one half year old growing practice located in a small community in central California (San Joaquin County). Excellent opportunity for a MD eager to take over a practice in a rapidly growing community. Terms flexible, includes equipment, building negotiable. Call Larry (209) 577-4983 after 6:00 pm.

SOUTHERN CALIFORNIA—INTERNAL MEDICINE practice for sale by well-established retiring physician. Also suitable for Family Practitioner. In desirable area 50 minutes east of Los Angeles. Contact Karlman Associates, (415) 391-1247.

OFFICE SPACE

SURGERY CENTER/MEDICAL OFFICE. Prime downtown San Francisco location, stunning decor professionally done, breathtaking views, prestigious waiting room, four exam/treatment rooms, two completely equipped operating rooms, recovery room, three business offices, kitchen, secretarial area, marble bathroom. Sale can be with or without equipment. 3,000 square feet total. Seven years remains on lease. Facility is three years old. This is a special prestigious facility being sold far below cost. Call Ken at (415) 398-2233.

MEDICAL OFFICE FOR LEASE. Fully equipped, prime downtown location. Fast growing area, walk to beach. Carlsbad, San Diego County, California. Reply to PO Box 4239, Carlsbad, CA 92008.

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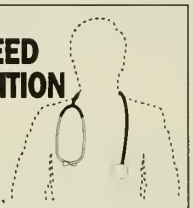

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Arizona Medical Association, Inc—810 W Bethany Home Rd, Phoenix 85013. (602) 246-8901. Annual Meeting: June 9-11, 1988, Loew's Ventana Canyon Resort, Tucson.

California Medical Association—PO Box 7690, San Francisco 94120-7690. (415) 541-0900. Annual Meeting: March 3-8, 1989, Disneyland Hotel, Anaheim.

Colorado Medical Society—PO Box 17550, Denver 80217-0550. (303) 779-5455. Annual Meeting: September 15-17, 1988, Marriott City Center, Denver.

Hawaii Medical Association—1360 S Beretania, Honolulu 96814. (808) 536-7702. Annual Meeting: October 10-12, 1987, Kauai Surf, Kauai.

Idaho Medical Association—305 W Jefferson, PO Box 2668, Boise 83701. (208) 344-7888. Annual Meeting: July 21-23, 1988, Sun Valley.

Montana Medical Association—2012 11th Ave, Suite 12, Helena 59601. (406) 443-4000. Annual Meeting: September 29-October 1, 1988, Heritage Inn, Great Falls.

Nevada State Medical Association—3660 Baker Lane, Reno 89502. (702) 825-6788. Annual Meeting: 1989, date and place to be announced.

New Mexico Medical Society—303 San Mateo NE, Suite 204, Albuquerque 87108. (505) 266-7868. Annual Meeting: May 5-7, 1988, Hilton Inn, Albuquerque.

Oregon Medical Association—5210 SW Corbett Ave, Portland 97201. (503) 226-1555. Annual Meeting: (House of Delegates only): November 6-8, 1987, Portland.

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Washington State Medical Association—900 United Airlines Bldg, 2033 6th Ave, Seattle 98121. (206) 441-WSMA. Annual Meeting: September 15-18, 1988, Yakima.

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ceftriaxone sodium/Roche

Before prescribing, please consult complete product information, a summary of which follows:

INDICATIONS AND USAGE: Rocephin is indicated for the treatment of the following infections when caused by susceptible organisms

LOWER RESPIRATORY TRACT INFECTIONS caused by *Strep. pneumoniae, Streptococcus* species (excluding enterococci), *Staph. aureus, H. influenzae, H. parainfluenzae, Klebsiella* species (including *K. pneumoniae*), *E. coli, E. aerogenes, Proteus mirabilis* and *Serratia marcescens*

SKIN AND SKIN STRUCTURE INFECTIONS caused by *Staph. aureus, Staph. epidermidis, Streptococcus* species (excluding enterococci), *E. cloacae, Klebsiella* species (including *K. pneumoniae*), *Proteus mirabilis* and *Pseudomonas aeruginosa*

URINARY TRACT INFECTIONS (complicated and uncomplicated) caused by *E. coli, Proteus mirabilis, Proteus vulgaris, M. morganii* and *Klebsiella* species (including *K. pneumoniae*)

UNCOMPLICATED GONORRHEA (cervical/urethral and rectal) caused by *Neisseria gonorrhoeae*, including both penicillinase and nonpenicillinase producing strains

PELVIC INFLAMMATORY DISEASE caused by *N. gonorrhoeae*

BACTERIAL SEPTICEMIA caused by *Staph. aureus, Strep. pneumoniae, E. coli, H. influenzae* and *K. pneumoniae*

BONE AND JOINT INFECTIONS caused by *Staph. aureus, Strep. pneumoniae, Streptococcus* species (excluding enterococci), *E. coli, P. mirabilis, K. pneumoniae* and *Enterobacter* species

INTRA-ABDOMINAL INFECTIONS caused by *E. coli* and *K. pneumoniae*

MENINGITIS caused by *H. influenzae, N. meningitidis* and *Strep. pneumoniae*. Ceftriaxone has also been used successfully in a limited number of cases of meningitis and shunt infections caused by *Staph. epidermidis* and *E. coli*

SURGICAL PROPHYLAXIS. Preoperative administration of a single 1 gm dose may reduce incidence of postoperative infections in patients undergoing surgical procedures classified as contaminated or potentially contaminated (e.g., vaginal or abdominal hysterectomy) and in those for whom infection at the operative site presents serious risk (e.g., during coronary artery bypass surgery).

Although ceftriaxone has been shown to have been as effective as cefazolin in the prevention of infection following coronary artery bypass surgery, no placebo-controlled trials have been conducted to evaluate any cephalosporin antibiotic in the prevention of infection following coronary artery bypass surgery. When administered before indicated surgical procedures, a single 1 gm dose provides protection from most infections due to susceptible organisms for duration of procedure.

SUSCEPTIBILITY TESTING. Before instituting treatment with Rocephin, appropriate specimens should be obtained for isolation of the causative organism and for determination of its susceptibility to the drug. Therapy may be instituted prior to obtaining results of susceptibility testing.

CONTRAINDICATIONS: Rocephin is contraindicated in patients with known allergy to the cephalosporin class of antibiotics.

WARNINGS: BEFORE THERAPY WITH ROCEPHIN IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE TO DETERMINE WHETHER THE PATIENT HAS HAD PREVIOUS HYPERSENSITIVITY REACTIONS TO CEPHALOSPORINS, PENICILLINS OR OTHER DRUGS. THIS PRODUCT SHOULD BE GIVEN CAUTIOUSLY TO PENICILLIN-SENSITIVE PATIENTS. ANTIBIOTICS SHOULD BE ADMINISTERED WITH CAUTION TO ANY PATIENT WHO HAS DEMONSTRATED SOME FORM OF ALLERGY PARTICULARLY TO DRUGS. SERIOUS ACUTE HYPERSENSITIVITY REACTIONS MAY REQUIRE THE USE OF SUBCUTANEOUS EPINEPHRINE AND OTHER EMERGENCY MEASURES.

Pseudomembranous colitis has been reported with the use of cephalosporins (and other broad-spectrum antibiotics), therefore, it is important to consider its diagnosis in patients who develop diarrhea in association with antibiotic use.

Treatment with broad-spectrum antibiotics alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate a toxin produced by *Clostridium difficile* is one primary cause of antibiotic-associated colitis. Cholestyramine and colestipol resins have been shown to bind to the toxin *in vitro*.

Mild cases of colitis respond to drug discontinuance alone. Moderate to severe cases should be managed with fluid, electrolyte and protein supplementation as indicated.

When the colitis is not relieved by drug discontinuance or when it is severe, oral vancomycin is the treatment of choice for antibiotic-associated pseudomembranous colitis produced by *C. difficile*. Other causes of colitis should also be considered.

Rarely, shadows suggesting sludge have been detected by sonograms of the gallbladder in asymptomatic and symptomatic patients. This appears to be reversible on discontinuation of therapy. In a few symptomatic patients receiving higher than usual doses, who underwent surgery, sludge containing traces of ceftriaxone was recovered from surgical specimens. Discontinue therapy in patients who develop signs or symptoms suggestive of gallbladder disease, consider conservative management.

PRECAUTIONS: *GENERAL*. Although transient elevations of BUN and serum creatinine have been observed, at the recommended dosages, the nephrotoxic potential of Rocephin is similar to that of other cephalosporins.

Ceftriaxone is excreted via both biliary and renal excretion (see Clinical Pharmacology). Therefore, patients with renal failure normally require no adjustment in dosage when usual doses of Rocephin are administered, but concentrations of drug in the serum should be monitored periodically. If evidence of accumulation exists, dosage should be decreased accordingly.

Dosage adjustments should not be necessary in patients with hepatic dysfunction, however, in patients with both hepatic dysfunction and significant renal disease, Rocephin dosage should not exceed 2 gm daily without close monitoring of serum concentrations.

Alterations in prothrombin times have occurred rarely in patients treated with Rocephin. Patients with impaired vitamin K synthesis or low vitamin K stores (e.g., chronic hepatic disease and malnutrition) may require monitoring of prothrombin time during Rocephin treatment. Vitamin K administration (10 mg weekly) may be necessary if the prothrombin time is prolonged before or during therapy.

Prolonged use of Rocephin may result in overgrowth of nonsusceptible organisms. Careful observation of the patient is essential. If superinfection occurs during therapy, appropriate measures should be taken.

Rocephin should be prescribed with caution in individuals with a history of gastrointestinal disease, especially colitis.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY. Carcinogenesis. Considering the maximum duration of treatment and the class of the compound, carcinogenicity studies with ceftriaxone in animals have not been performed. The maximum

duration of animal toxicity studies was six months.

Mutagenesis. Genetic toxicology tests included the Ames test, a micronucleus test and a test for chromosomal aberrations in human lymphocytes cultured *in vitro* with ceftriaxone. Ceftriaxone showed no potential for mutagenic activity in these studies.

Impairment of Fertility. Ceftriaxone produced no impairment of fertility when given intravenously to rats at daily doses up to 586 mg/kg/day, approximately 20 times the recommended clinical dose of 2 gm/day.

PREGNANCY. Teratogenic Effects. Pregnancy Category B. Reproductive studies have been performed in mice and rats at doses up to 20 times the usual human dose and have no evidence of embryotoxicity, fetotoxicity or teratogenicity. In primates, no embryotoxicity or teratogenicity was demonstrated at a dose approximately three times the human dose.

There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproductive studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nonteratogenic Effects. In rats, in the Segment I (fertility and general reproduction) and Segment III (perinatal and postnatal) studies with intravenously administered ceftriaxone, no adverse effects were noted on various reproductive parameters during gestation and lactation, including postnatal growth, functional behavior and reproductive ability of the offspring at doses of 586 mg/kg/day or less.

NURSING MOTHERS. Low concentrations of ceftriaxone are excreted in human milk. Caution should be exercised when Rocephin is administered to a nursing woman.

PEDIATRIC USE. Safety and effectiveness of Rocephin in neonates, infants and children have been established for the dosages described in the Dosage and Administration section. *In vitro* studies have shown ceftriaxone, like some other cephalosporins, can displace bilirubin from serum albumin. Exercise caution before administration to hyperbilirubinemic neonates, especially prematures.

ADVERSE REACTIONS: Rocephin is generally well tolerated. In clinical trials, the following adverse reactions, which were considered to be related to Rocephin therapy or of uncertain etiology, were observed:

LOCAL REACTIONS—pain, induration or tenderness at the site of injection (1%). Less frequently reported (less than 1%) was phlebitis after I.V. administration.

HYPERSENSITIVITY—rash (1.7%). Less frequently reported (less than 1%) were pruritus, fever or chills.

HEMATOLOGIC—eosinophilia (6%), thrombocytosis (5.1%) and leukopenia (2.1%). Less frequently reported (less than 1%) were anemia, neutropenia, lymphopenia, thrombocytopenia and prolongation of the prothrombin time.

GASTROINTESTINAL—diarrhea (2.7%). Less frequently reported (less than 1%) were nausea or vomiting, and dysgeusia.

HEPATIC—elevations of SGOT (3.1%) or SGPT (3.3%). Less frequently reported (less than 1%) were elevations of alkaline phosphatase and bilirubin.

RENAL—elevations of the BUN (1.2%). Less frequently reported (less than 1%) were elevations of creatinine and the presence of casts in the urine.

CENTRAL NERVOUS SYSTEM—headache or dizziness were reported occasionally (less than 1%).

GENITOURINARY—moniliasis or vaginitis were reported occasionally (less than 1%).

MISCELLANEOUS—diaphoresis and flushing were reported occasionally (less than 1%).

Other rarely observed adverse reactions (less than 0.1%) include leukocytosis, lymphocytosis, monocytosis, basophilia, a decrease in the prothrombin time, jaundice, gallbladder sludge, glycosuria, hematuria, anaphylaxis, bronchospasm, serum sickness, abdominal pain, colitis, flatulence, dyspepsia, palpitations and epistaxis.

DOSAGE AND ADMINISTRATION: Rocephin may be administered intravenously or intramuscularly. The usual adult daily dose is 1 to 2 gm given once a day (or in equally divided doses twice a day) depending on the type and severity of the infection. The total daily dose should not exceed 4 grams.

For the treatment of serious miscellaneous infections in children, other than meningitis, the recommended total daily dose is 50 to 75 mg/kg (not to exceed 2 grams), given in divided doses every 12 hours.

Generally, Rocephin therapy should be continued for at least two days after the signs and symptoms of infection have disappeared. The usual duration is 4 to 14 days, in complicated infections longer therapy may be required.

In the treatment of meningitis, a daily dose of 100 mg/kg (not to exceed 4 grams), given in divided doses every 12 hours, should be administered with or without a loading dose of 75 mg/kg.

For the treatment of uncomplicated gonococcal infections, a single intramuscular dose of 250 mg is recommended.

For preoperative use (surgical prophylaxis), a single dose of 1 gm administered 1/2 to 2 hours before surgery is recommended.

When treating infections caused by *Streptococcus pyogenes*, therapy should be continued for at least ten days.

No dosage adjustment is necessary for patients with impairment of renal or hepatic function, however, blood levels should be monitored in patients with severe renal impairment (e.g., dialysis patients) and in patients with both renal and hepatic dysfunctions.

HOW SUPPLIED: Rocephin (ceftriaxone sodium/Roche) is supplied as a sterile crystalline powder in glass vials and piggyback bottles. The following packages are available:

Vials containing 250 mg, 500 mg, 1 gm or 2 gm equivalent of ceftriaxone, piggyback bottles containing 1 gm or 2 gm equivalent of ceftriaxone, bulk pharmacy containers containing 10 gm equivalent of ceftriaxone (NOT FOR DIRECT ADMINISTRATION).

Also supplied as a sterile crystalline powder as follows:

ADD-Vantage Vials** containing 1 gm or 2 gm equivalent of ceftriaxone.

Also supplied premixed as a frozen iso-osmotic, sterile, nonpyrogenic solution of ceftriaxone sodium in 50 mL single dose plastic containers,† as follows:

1 gm equivalent of ceftriaxone, iso-osmotic with approximately 1.9 gm dextrose hydrous, USP added.

2 gm equivalent of ceftriaxone, iso-osmotic with approximately 1.2 gm dextrose hydrous, USP added.

NOTE: Rocephin in the frozen state should not be stored above -20°C.

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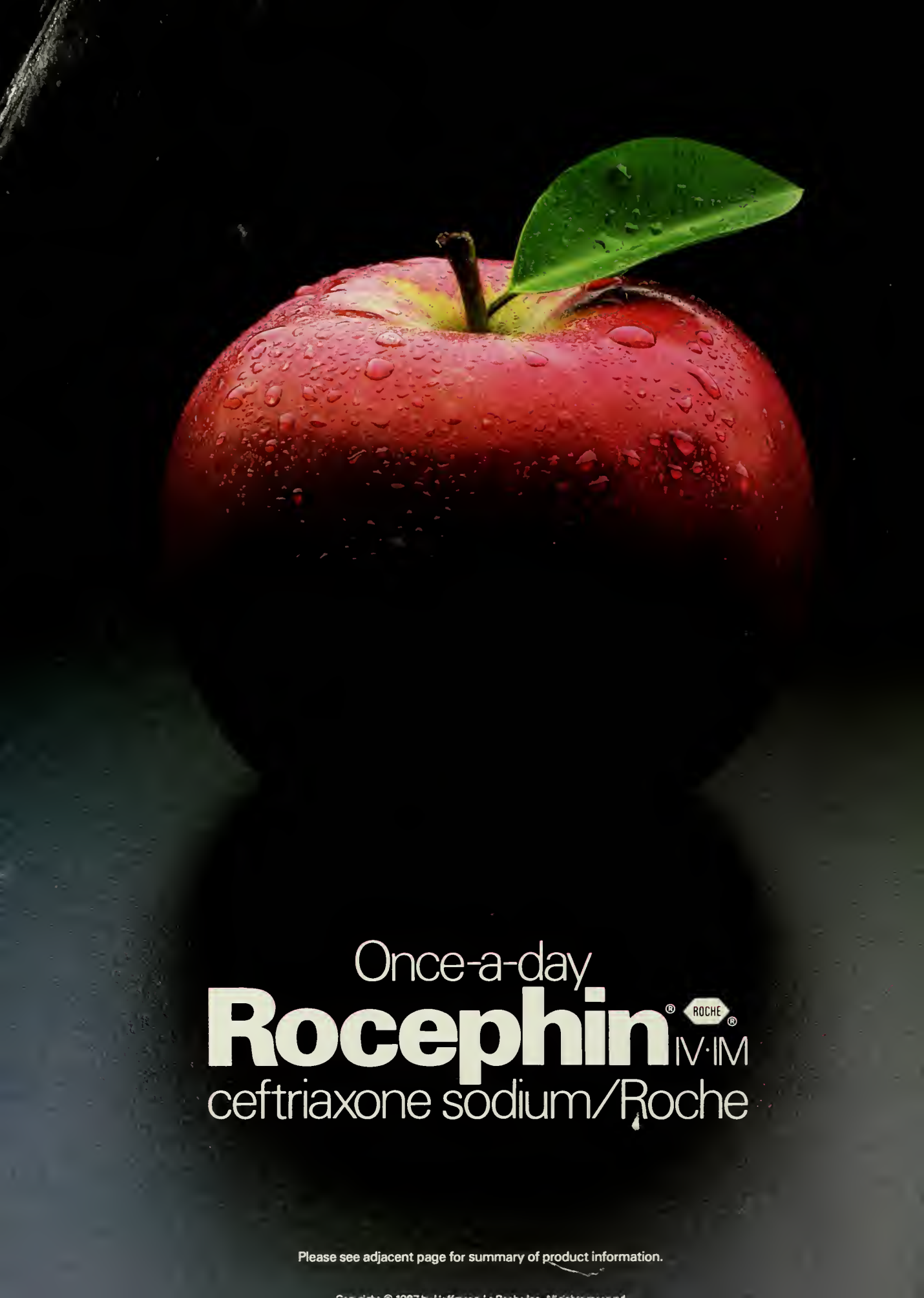
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ZOVIRAX®
(acyclovir)
CAPSULES
Prevent genital herpes recurrences month after month with daily therapy.
(In controlled studies, recurrences were totally prevented for 4 to 6 months in up to 75% of patients.)
Please see last page of this advertisement for brief summary of prescribing information.

ZOVIRAX® (acyclovir) CAPSULES

Help free your patients from recurrences.

Daily therapy

Coping with genital herpes is rarely easy. For some, the worst part is the pain and discomfort of frequent attacks —month after month, year after year. For others, the emotional burden presents a more difficult problem, leading to social isolation, anxiety, and diminished self-esteem.

Prevent or reduce recurrences

Although your patients have to live with herpes, they shouldn't have to suffer. Daily therapy with ZOVIRAX CAPSULES can help free them from the cycle of recurrent genital herpes. For many, one capsule three times a day can suppress recurrences completely while on therapy.

Generally well tolerated

Daily therapy with ZOVIRAX CAPSULES is generally well tolerated. The most frequent adverse reactions reported during clinical trials were headache, diarrhea, nausea/vomiting, vertigo, and arthralgia.

The physical and emotional difficulties posed by genital herpes are unique for each patient. The frequency and severity of recurrent episodes, as well as the emotional impact of the disease, should be considered when selecting daily therapy with ZOVIRAX CAPSULES.

Please see brief summary of prescribing information on next page.

86-ZOV

Prevent recurrences month after month*

ZOVIRAX® (acyclovir) CAPSULES

Brief Summary

INDICATIONS AND USAGE: Zovirax Capsules are indicated for the treatment of initial episodes and the management of recurrent episodes of genital herpes in certain patients.

The severity of disease is variable depending upon the immune status of the patient, the frequency and duration of episodes, and the degree of cutaneous or systemic involvement. These factors should determine patient management, which may include symptomatic support and counseling only, or the institution of specific therapy. The physical, emotional and psycho-social difficulties posed by herpes infections as well as the degree of debilitation, particularly in immunocompromised patients, are unique for each patient, and the physician should determine therapeutic alternatives based on his or her understanding of the individual patient's needs. Thus Zovirax Capsules are not appropriate in treating all genital herpes infections. The following guidelines may be useful in weighing the benefit/risk considerations in specific disease categories:

First Episodes (primary and nonprimary infections — commonly known as initial genital herpes):

Double-blind, placebo-controlled studies have demonstrated that orally administered Zovirax significantly reduced the duration of acute infection (detection of virus in lesions by tissue culture) and lesion healing. The duration of pain and new lesion formation was decreased in some patient groups. The promptness of initiation of therapy and/or the patient's prior exposure to Herpes simplex virus may influence the degree of benefit from therapy. Patients with mild disease may derive less benefit than those with more severe episodes. In patients with extremely severe episodes, in which prostration, central nervous system involvement, urinary retention or inability to take oral medication require hospitalization and more aggressive management, therapy may be best initiated with intravenous Zovirax.

Recurrent Episodes:

Double-blind, placebo-controlled studies in patients with frequent recurrences (6 or more episodes per year) have shown that Zovirax Capsules given for 4 to 6 months prevented or reduced the frequency and/or severity of recurrences in greater than 95% of patients. Clinical recurrences were prevented in 40 to 75% of patients. Some patients experienced increased severity of the first episode following cessation of therapy; the severity of subsequent episodes and the effect on the natural history of the disease are still under study.

The safety and efficacy of orally administered acyclovir in the suppression of frequent episodes of genital herpes have been established only for up to 6 months. Chronic suppressive therapy is most appropriate when, in the judgement of the physician, the benefits of such a regimen outweigh known or potential adverse effects. In general, Zovirax Capsules should not be used for the suppression of recurrent disease in mildly affected patients. Unanswered questions concerning the human relevance of *in vitro* mutagenicity studies and reproductive toxicity studies in animals given very high doses of acyclovir for short periods (see Carcinogenesis, Mutagenesis, Impairment of Fertility) should be borne in mind when designing long-term management for individual patients. Discussion of these issues with patients will provide them the opportunity to weigh the potential for toxicity against the severity of their disease. Thus, this regimen should be considered only for appropriate patients and only for six months until the results of ongoing studies allow a more precise evaluation of the benefit/risk assessment of prolonged therapy.

Limited studies have shown that there are certain patients for whom intermittent short-term treatment of recurrent episodes is effective. This approach may be more appropriate than a suppressive regimen in patients with infrequent recurrences.

Immunocompromised patients with recurrent herpes infections can be treated with either intermittent or chronic suppressive therapy. Clinically significant resistance, although rare, is more likely to be seen with prolonged or repeated therapy in severely immunocompromised patients with active lesions.

CONTRAINDICATIONS: Zovirax Capsules are contraindicated for patients who develop hypersensitivity or intolerance to the components of the formulation.

WARNINGS: Zovirax Capsules are intended for oral ingestion only.

PRECAUTIONS: General: Zovirax has caused decreased spermatogenesis at high doses in some animals and mutagenesis in some acute studies at high concentrations of drug (see PRECAUTIONS — Carcinogenesis, Mutagenesis, Impairment of Fertility). The recommended dosage and length of treatment should not be exceeded (see DOSAGE AND ADMINISTRATION).

Exposure of Herpes simplex isolates to acyclovir *in vitro* can lead to the emergence of less sensitive viruses. The possibility of the appearance of less sensitive viruses in man must be borne in mind when treating patients. The relationship between the *in vitro* sensitivity of Herpes simplex virus to acyclovir and clinical response to therapy has yet to be established.

Because of the possibility that less sensitive virus may be selected in patients who are receiving acyclovir, all patients should be advised to take particular care to avoid potential transmission of virus if active lesions are present while they are on therapy. In severely immunocompromised patients, the physician should be aware that prolonged or repeated courses of acyclovir may result in selection of resistant viruses which may not fully respond to continued acyclovir therapy.

Drug Interactions: Co-administration of probenecid with intravenous acyclovir has been shown to increase the mean half-life and the area under the concentration-time curve. Urinary excretion and renal clearance were correspondingly reduced.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Acyclovir was tested in lifetime bioassays in rats and mice at single daily doses of 50, 150 and 450 mg/kg given by gavage. There was no statistically significant difference in the incidence of tumors between treated and control animals, nor did acyclovir shorten the latency of tumors. In 2 *in vitro* cell transformation assays, used to provide preliminary assessment of potential oncogenicity in advance of these more definitive life-time bioassays in rodents, conflicting results were obtained. Acyclovir was positive at the highest dose used in one system and the resulting morphologically transformed cells formed tumors when inoculated into immunosuppressed, syngeneic, weanling mice. Acyclovir was negative in another transformation system considered less sensitive.

In acute studies, there was an increase, not statistically significant, in the incidence of chromosomal damage at maximum tolerated parenteral doses of 100 mg/kg acyclovir in rats but not Chinese hamsters; higher doses of 500 and 1000 mg/kg were clastogenic in Chinese hamsters. In addition, no activity was found after 5 days dosing in a dominant lethal study in mice. In 6 of 11 microbial and mammalian cell assays, no evidence of mutagenicity was observed. At 3 loci in a Chinese hamster ovary cell line, the results were inconclusive. In 2 mammalian cell assays (human lymphocytes and L5178Y mouse lymphoma cells *in vitro*), positive responses for mutagenicity and chromosomal damage occurred, but only at concentrations at least 400 times the acyclovir plasma levels achieved in man.

Acyclovir has not been shown to impair fertility or reproduction in mice (450 mg/kg/day, p.o.) or in rats (25 mg/kg/day, s.c.). At 50 mg/kg/day s.c. in the rat, there was a statistically significant increase in post-implantation loss, but no concomitant decrease in litter size. In female rabbits treated subcutaneously with acyclovir subsequent to mating, there was a statistically significant decrease in implantation efficiency but no concomitant decrease in litter size at a dose of 50 mg/kg/day. No effect upon implantation efficiency was observed when the same dose was administered intravenously. In a rat peri- and postnatal study at 50 mg/kg/day s.c., there was a statistically significant decrease in the group mean numbers of corpora lutea, total implantation sites and live fetuses in the F_1 generation. Although not statistically significant, there was also a dose related decrease in group mean numbers of live fetuses and implantation sites at 12.5 mg/kg/day and 25 mg/kg/day, s.c. The intravenous administration of 100 mg/kg/day, a dose known to cause obstructive nephropathy in rabbits, caused a significant increase in fetal resorptions and a corresponding decrease in litter size. However, at a maximum tolerated intravenous dose of 50 mg/kg/day in rabbits, there were no drug-related reproductive effects.

Intraperitoneal doses of 320 or 80 mg/kg/day acyclovir given to rats for 1 and 6 months, respectively, caused testicular atrophy. Testicular atrophy was persistent through the 4-week postdose recovery phase after 320 mg/kg/day; some evidence of recovery of sperm production was evident 30 days postdose. Intravenous doses of 100 and 200 mg/kg/day acyclovir given to dogs for 31 days caused aspermatogenesis. Testicles were normal in dogs given 50 mg/kg/day, i.v. for one month.

Pregnancy: ***Teratogenic Effects:*** Pregnancy Category C. Acyclovir was not teratogenic in the mouse (450 mg/kg/day, p.o.), rat (50 mg/kg/day, s.c.) or rabbit (50 mg/kg/day, s.c. and i.v.). There are no adequate and well-controlled studies in pregnant women. Acyclovir should not be used during pregnancy unless the potential benefit justifies the potential risk to the fetus. Although acyclovir was not teratogenic in animal studies, the drug's potential for causing chromosome breaks at high concentration should be taken into consideration in making this determination.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Zovirax is administered to a nursing woman. In nursing mothers, consideration should be given to not using acyclovir treatment or discontinuing breastfeeding.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS — Short-Term Administration: The most frequent adverse reactions reported during clinical trials were nausea and/or vomiting in 8 of 298 patient treatments (2.7%) and headache in 2 of 298 (0.6%). Less frequent adverse reactions, each of which occurred in 1 of 298 patient treatments (0.3%), included diarrhea, dizziness, anorexia, fatigue, edema, skin rash, leg pain, inguinal adenopathy, medication taste and sore throat.

Long-Term Administration: The most frequent adverse reactions reported in studies of daily therapy for 3 to 6 months were headache in 33 of 251 patients (13.1%), diarrhea in 22 of 251 (8.8%), nausea and/or vomiting in 20 of 251 (8.0%), vertigo in 9 of 251 (3.6%), and arthralgia in 9 of 251 (3.6%). Less frequent adverse reactions, each of which occurred in less than 3% of the 251 patients (see number of patients in parentheses), included skin rash (7), insomnia (4), fatigue (7), fever (4), palpitations (1), sore throat (2), superficial thrombophlebitis (1), muscle cramps (2), pars planitis (1), menstrual abnormality (4), acne (3), lymphadenopathy (2), irritability (1), accelerated hair loss (1), and depression (1).

DOSAGE AND ADMINISTRATION: Treatment of initial genital herpes: One 200 mg capsule every 4 hours, while awake, for a total of 5 capsules daily for 10 days (total 50 capsules).

Chronic suppressive therapy for recurrent disease: One 200 mg capsule 3 times daily for up to 6 months. Some patients may require more drug, up to one 200 mg capsule 5 times daily for up to 6 months.

Intermittent Therapy: One 200 mg capsule every 4 hours, while awake, for a total of 5 capsules daily for 5 days (total 25 capsules). Therapy should be initiated at the earliest sign or symptom (prodrome) of recurrence.

Patients With Acute or Chronic Renal Impairment: One 200 mg capsule every 12 hours is recommended for patients with creatinine clearance ≤ 10 ml/min/1.73/m^2.

HOW SUPPLIED: Zovirax Capsules (blue, opaque) containing 200 mg acyclovir and printed with "Wellcome ZOVIRAX 200" - Bottles of 100 (NDC-0081-0991-55) and unit dose pack of 100 (NDC-0081-0991-56).

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*In controlled studies, recurrences were totally prevented for 4 to 6 months in up to 75% of patients.

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IMPROVING LIVES THROUGH ANTIVIRAL RESEARCH

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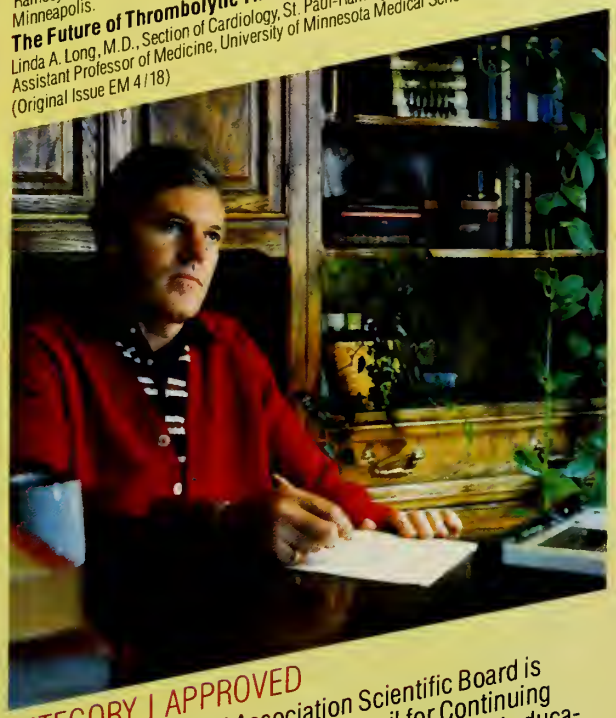

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IN HYPERTENSION*

QUALITY

***CAPOTEN® (captopril tablets) may be used as initial therapy only for patients with normal renal function in whom the risk of neutropenia/agranulocytosis is relatively low (1 out of over 8,600 in clinical trials). Use special precautions in patients with impaired renal function, collagen vascular disorders, or those exposed to other drugs known to affect the white cells or immune response. Evaluation of hypertensives should always include assessment of renal function. Overall, the most frequently occurring adverse reactions associated with CAPOTEN are skin rash and taste alteration; both effects are generally mild, reversible, or self-limited. See INDICATIONS AND USAGE, WARNINGS, and ADVERSE REACTIONS in the brief summary on the adjacent page.**

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1. Croog SH, Levine S, Testa MA, et al: The effects of antihypertensive therapy on the quality of life. N Engl J Med 314(26):1657-1664, 1986.
2. Data on file, University of Connecticut.

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CONTRAINDICATIONS: CAPOTEN is contraindicated in patients who are hypersensitive to this product.

WARNINGS: Neutropenia/Agranulocytosis — Neutropenia (< 1000/mm³) with myeloid hypoplasia has resulted from use of captopril. About half of the neutropenic patients developed systemic or oral cavity infections or other features of the syndrome of agranulocytosis. The risk of neutropenia is dependent on the clinical status of the patient:

In clinical trials in patients with hypertension who have normal renal function (serum creatinine less than 1.6 mg/dL and no collagen vascular disease), neutropenia has been seen in one patient out of over 8,600 exposed. In patients with some degree of renal failure (serum creatinine at least 1.6 mg/dL) but no collagen vascular disease, the risk in clinical trials was about 1 per 500. Doses were relatively high in these patients, particularly in view of their diminished renal function. In patients with collagen vascular diseases (e.g., systemic lupus erythematosus, scleroderma) and impaired renal function, neutropenia occurred in 3.7% of patients in clinical trials. While none of the over 750 patients in formal clinical trials of heart failure developed neutropenia, it has occurred during the subsequent clinical experience. Of reported cases, about half had serum creatinine ≥ 1.6 mg/dL and more than 75% received procainamide. In heart failure, it appears that the same risk factors for neutropenia are present.

Neutropenia has appeared usually within 3 months after starting therapy, associated with myeloid hypoplasia and frequently accompanied by erythroid hypoplasia and decreased numbers of megakaryocytes (e.g., hypoplastic bone marrow and pancytopenia); anemia and thrombocytopenia were sometimes seen. Neutrophils generally returned to normal in about 2 weeks after captopril was discontinued, and serious infections were limited to clinically complex patients. About 13% of the cases of neutropenia have ended fatally, but almost all fatalities were in patients with serious illness, having collagen vascular disease, renal failure, heart failure or immunosuppressant therapy, or a combination of these complicating factors. **Evaluation of the hypertensive or heart failure patient should always include assessment of renal function.** If captopril is used in patients with impaired renal function, white blood cell and differential counts should be evaluated prior to starting treatment and at approximately 2-week intervals for about 3 months, then periodically. In patients with collagen vascular disease or who are exposed to other drugs known to affect the white cells or immune response, particularly when there is impaired renal function, captopril should be used only after an assessment of benefit and risk, and then with caution. All patients treated with captopril should be told to report any signs of infection (e.g., sore throat, fever). If infection is suspected, perform white cell counts without delay. Since discontinuation of captopril and other drugs has generally led to prompt return of the white count to normal, upon confirmation of neutropenia (neutrophil count < 1000/mm³) withdraw captopril and closely follow the patient's course.

Proteinuria: Total urinary proteins > 1 g per day were seen in about 0.7% of patients on captopril. About 90% of affected patients had evidence of prior renal disease or received high doses (> 150 mg/day), or both. The nephrotic syndrome occurred in about one-fifth of proteinuric patients. In most cases, proteinuria subsided or cleared within 6 months whether or not captopril was continued. The BUN and creatinine were seldom altered in proteinuric patients. Since most cases of proteinuria occurred by the 8th month of therapy with captopril, patients with prior renal disease or those receiving captopril at doses > 150 mg per day, should have urinary protein estimates (dip-stick on 1st morning urine) before therapy, and periodically thereafter.

Hypotension: Excessive hypotension was rarely seen in hypertensive patients but is a possibility in severely salt/volume-depleted persons such as those treated vigorously with diuretics (see PRECAUTIONS [Drug Interactions]). In heart failure, where the blood pressure was either normal or low, transient decreases in mean blood pressure > 20% were recorded in about half of the patients. This transient hypotension may occur after any of the first several doses and is usually well tolerated, although rarely it has been associated with arrhythmia or conduction defects. A starting dose of 6.25 or 12.5 mg tid may minimize the hypotensive effect. Patients should be followed closely for the first 2 weeks of treatment and whenever the dose of captopril and/or diuretic is increased.

BECAUSE OF THE POTENTIAL FALL IN BLOOD PRESSURE IN THESE PATIENTS, THERAPY SHOULD BE STARTED UNDER VERY CLOSE MEDICAL SUPERVISION.

PRECAUTIONS: General: *Impaired Renal Function* — Hypertension — Some hypertensive patients with renal disease, particularly those with severe renal artery stenosis, have developed increases in BUN and serum creatinine. It may be necessary to reduce captopril dosage and/or discontinue diuretic. For some of these patients, normalization of blood pressure and maintenance of adequate renal perfusion may not be possible. Heart Failure — About 20% of patients develop stable elevations of BUN and serum creatinine > 20% above normal or baseline upon long-term treatment. Less than 5% of patients, generally with severe preexisting renal disease, required discontinuation due to progressively increasing creatinine. See DOSAGE AND ADMINISTRATION, ADVERSE REACTIONS [Altered Laboratory Findings]. *Valvular Stenosis* — A theoretical concern, for risk of decreased coronary perfusion, has been noted regarding vasodilator treatment in patients with aortic stenosis due to decreased afterload reduction. *Surgery/Anesthesia* — If hypotension occurs during surgery or anesthesia, and is considered due to the effects of captopril, it is correctable by volume expansion.

Drug Interactions: *Hypotension — Patients on Diuretic Therapy* — Precipitous reduction of blood pressure may occasionally occur within the 1st hour after administration of the initial of captopril dose in patients on diuretics, especially those recently placed on diuretics, and those on severe dietary salt restriction or dialysis. This possibility can be minimized by either discontinuing the diuretic or increasing the salt intake about 1 week prior to initiation of captopril therapy or by initiating therapy with small doses (6.25 or 12.5 mg). Alternatively, provide medical supervision for at least 1 hour after the initial dose.

Agents Having Vasodilator Activity — In heart failure patients, vasodilators should be administered with caution.

Agents Causing Renin Release — Captopril's effect will be augmented by antihypertensive agents that cause renin release.

Agents Affecting Sympathetic Activity — The sympathetic nervous system may be especially important in supporting blood pressure in patients receiving captopril alone or with diuretics. Beta-adrenergic blocking drugs add some further antihypertensive effect to captopril, but the overall response is less than additive. Therefore, use agents affecting sympathetic activity (e.g., ganglionic blocking agents or adrenergic neuron blocking agents) with caution.

Agents Increasing Serum Potassium — Give potassium-sparing diuretics or potassium supplements only for documented hypokalemia, and then with caution, since they may lead to a significant increase of serum potassium. Use potassium-containing salt substitutes with caution.

Inhibitors of Endogenous Prostaglandin Synthesis — Indomethacin and other nonsteroidal anti-inflammatory agents may reduce the antihypertensive effect of captopril, especially in low renin hypertension.

Drug/Laboratory Test Interaction: Captopril may cause a false-positive urine test for acetone.

Carcinogenesis, Mutagenesis and Impairment of Fertility: Two-year studies with doses of 50 to 1350 mg/kg/day in mice and rats failed to show any evidence of carcinogenic potential. Studies in rats have revealed no impairment of fertility.

Pregnancy: Category C: There are no adequate and well-controlled studies in pregnant women. Embryocidal effects and craniofacial malformations were observed in rabbits. Therefore, captopril should be used during pregnancy, or for patients likely to become pregnant, only if the potential benefit outweighs the potential risk to the fetus. Captopril crosses the human placenta.

Nursing Mothers: Captopril is secreted in human milk. Exercise caution when administering captopril to a nursing woman, and, in general, nursing should be interrupted.

Pediatric Use: Safety and effectiveness in children have not been established although there is limited experience with use of captopril in children from 2 months to 15 years of age. Dosage, on a weight basis, was comparable to that used in adults. CAPOTEN (captopril) should be used in children only if other measures for controlling blood pressure have not been effective.

ADVERSE REACTIONS: Reported incidences are based on clinical trials involving approximately 7000 patients.

Renal — About 1 of 100 patients developed proteinuria (see WARNINGS). Renal insufficiency, renal failure, polyuria, oliguria, and urinary frequency in 1 to 2 of 1000 patients.

Hematologic — Neutropenia/agranulocytosis has occurred (see WARNINGS). Anemia, thrombocytopenia, and pancytopenia have been reported.

Dermatologic — Rash, (usually maculopapular, rarely urticarial), often with pruritus, and sometimes with fever and eosinophilia, in about 4 to 7 of 100 patients (depending on renal status and dose), usually during the 1st 4 weeks of therapy. Pruritus, without rash, in about 2 of 100 patients. A reversible associated pemphigoid-like lesion, and photosensitivity, have also been reported. Angioedema of the face, mucous membranes of the mouth, or of the extremities in about 1 of 1000 patients — reversible on discontinuance of captopril therapy. One case of laryngeal edema has been reported. Flushing or pallor in 2 to 5 of 1000 patients.

Cardiovascular — Hypotension may occur; see WARNINGS and PRECAUTIONS [Drug Interactions] for discussion of hypotension on initiation of captopril therapy. Tachycardia, chest pain, and palpitations each in about 1 of 100 patients. Angina pectoris, myocardial infarction, Raynaud's syndrome, and congestive heart failure each in 2 to 3 of 1000 patients.

Dysgeusia — Approximately 2 to 4 (depending on renal status and dose) of 100 patients developed a diminution or loss of taste perception; taste impairment is reversible and usually self-limited even with continued drug use (2 to 3 months). Gastric irritation, abdominal pain, nausea, vomiting, diarrhea, anorexia, constipation, aphthous ulcers, peptic ulcer, dizziness, headache, malaise, fatigue, insomnia, dry mouth, dyspnea, cough, alopecia, paresthesias reported in about 0.5 to 2% of patients but did not appear at increased frequency compared to placebo or other treatments used in controlled trials.

Altered Laboratory Findings: Elevations of liver enzymes in a few patients although no causal relationship has been established. Rarely cholestatic jaundice, and hepatocellular injury with or without secondary cholestasis, have been reported. A transient elevation of BUN and serum creatinine may occur, especially in volume-depleted or renovascular hypertension patients. In instances of rapid reduction of longstanding or severely elevated blood pressure, the glomerular filtration rate may decrease transiently, also resulting in transient rises in serum creatinine and BUN. Small increases in serum potassium concentration frequently occur, especially in patients with renal impairment (see PRECAUTIONS).

OVERDOSAGE: Primary concern is correction of hypotension. Volume expansion with an I.V. infusion of normal saline is the treatment of choice for restoration of blood pressure. Captopril may be removed from the general circulation by hemodialysis.

DOSAGE AND ADMINISTRATION: CAPOTEN (captopril) should be taken one hour before meals. In hypertension, CAPOTEN may be dosed bid or tid. Dosage must be individualized; see DOSAGE AND ADMINISTRATION section of package insert for detailed information regarding dosage in hypertension and in heart failure. Because CAPOTEN (captopril) is excreted primarily by the kidneys, dosage adjustments are recommended for patients with impaired renal function.

Consult package insert before prescribing CAPOTEN (captopril).

HOW SUPPLIED: Available in tablets of 12.5, 25, 50, and 100 mg in bottles of 100 (25 mg and 50 mg also available in bottles of 1000), and in UNIMATIC® unit-dose packs of 100 tablets. (J3-658J)

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The portrait of anxiety

Upjohn The Upjohn Company
Kalamazoo, Michigan 49001 USA

Please see adjacent page for brief summary of prescribing information.

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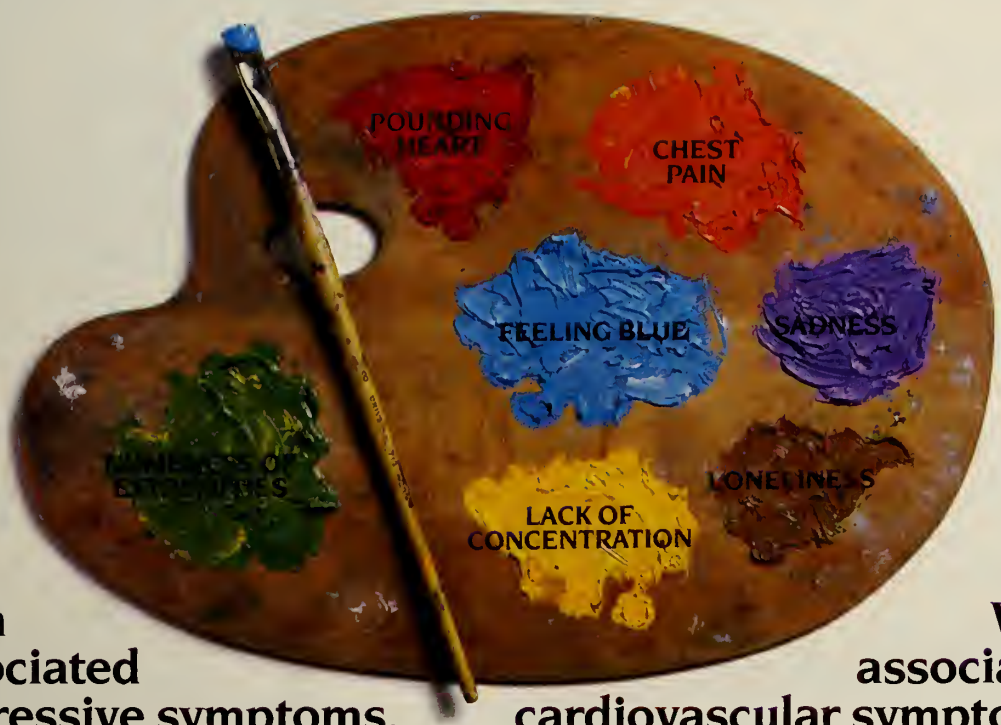
is often complicated



With associated depressive symptoms.

In double-blind, four-week clinical trials in 632 patients with moderate to severe anxiety, therapy with XANAX was compared with placebo.

XANAX was significantly more effective ($P<.001$) than placebo in relieving the anxiety, with over half of the patients showing marked to moderate improvement by the first evaluation period (one week).

In addition, over 70% of these patients experienced associated moderate to severe depressed mood. XANAX was shown to be significantly more effective ($P<.014$) than placebo in improving the associated depressed mood.

With associated cardiovascular symptoms.

Almost 60% of patients in the study had anxiety with associated cardiovascular symptoms even though cardiovascular disease had been ruled out. XANAX was shown to effectively relieve anxiety including the associated cardiovascular symptoms.

XANAX, the first of a unique class—the triazolobenzodiazepines.

- *Well tolerated*—Side effects, if they occur, are generally observed at the beginning of therapy and usually disappear with continued medication. Drowsiness and light-headedness were the most commonly reported adverse reactions.
- *Sustained efficacy*—No reported increase in dosage during 16-week clinical study, once an appropriate dosage was achieved. Since long-term effectiveness of XANAX has not been established, it is recommended that it not be used for longer than 16 weeks.
- *Simple dosage*—0.25 to 0.5 mg t.i.d.

TABLETS 0.25, 0.5 & 1 MG

Xanax®

alprazolam IV

for the relief of complicated anxiety

XANAX® Tablets
(alprazolam) ©

INDICATIONS AND USAGE
Anxiety disorders, short-term relief of the symptoms of anxiety, and anxiety associated with depression. Anxiety or tension associated with the stress of everyday life usually does not require an anxiolytic. Effectiveness for more than four months has not been established; periodically reassess the usefulness of the drug for the individual patient.

CONTRAINDICATIONS
Sensitivity to XANAX or other benzodiazepines, and in acute narrow angle glaucoma.

WARNINGS
Benzodiazepines can cause fetal harm in pregnant women, hence women who may become pregnant should be warned. Avoid during the first trimester. Withdrawal seizures have been reported upon rapid dose reduction or abrupt discontinuation, thus reduce dose gradually. (See Drug Abuse and Dependence and Dosage and Administration.)

PRECAUTIONS
General: If XANAX is combined with other psychotropics or anticonvulsants, consider drug potentiation. (See Drug Interactions). Use the usual precautions in patients with renal or hepatic impairment and regarding prescription size in depressed and suicidal patients. In elderly and debilitated patients, use the lowest possible dose. (See Dosage and Administration.) Hypomania and mania has been reported in depressed patients.

Information for Patients: Alert patients about: (a) consumption of alcohol and drugs, (b) possible fetal abnormalities, (c) operating machinery or driving, (d) not increasing dose of the drug due to risk of dependence, (e) not stopping the drug abruptly. *Laboratory Tests*: Not ordinarily required in otherwise healthy patients. *Drug Interactions*: Additive CNS depressant effects with other psychotropics, anticonvulsants, antihistamines, ethanol and other CNS depressants. Plasma levels of imipramine and desipramine are increased. Pharmacokinetic interactions with other drugs have been reported. Cimetidine can delay clearance of benzodiazepines. *Drug/Laboratory Test Interactions*: No consistent pattern for a drug or test. *Carcinogenesis, Mutagenesis, Impairment of Fertility*: No carcinogenic potential or impairment of fertility in rats. *Pregnancy*: See Warnings. *Nonteratogenic Effects*: The child born of a mother on benzodiazepines may be at some risk for withdrawal symptoms, neonatal flaccidity and respiratory problems. *Labor and Delivery*: No established use. *Nursing Mothers*: Benzodiazepines are excreted in human milk. Women on XANAX should not nurse. *Pediatric Use*: Safety and effectiveness in children below the age of 18 have not been established.

ADVERSE REACTIONS
Side effects are generally observed at the beginning of therapy and usually disappear with continued medication. In the usual patient, the most frequent side effects are likely to be an extension of the pharmacologic activity of XANAX, e.g., drowsiness or lightheadedness.

Central nervous system: Drowsiness, lightheadedness, depression, headache, confusion, insomnia, nervousness, syncope, dizziness, akathisia, and tiredness/sleepiness. *Gastrointestinal*: Dry mouth, constipation, diarrhea, nausea/vomiting, and increased salivation. *Cardiovascular*: Tachycardia/palpitations, and hypotension. *Sensory*: Blurred vision. *Musculoskeletal*: Rigidity and tremor. *Cutaneous*: Dermatitis/allergy. *Other side effects*: Nasal congestion, weight gain, and weight loss.

Withdrawal seizures with rapid decrease or abrupt discontinuation. (See Warnings.)

The following adverse events have been reported with benzodiazepines: dystonia, irritability, concentration difficulties, anorexia, transient amnesia or memory impairment, loss of coordination, fatigue, seizures, sedation, slurred speech, jaundice, musculoskeletal weakness, pruritus, diplopia, dysarthria, changes in libido, menstrual irregularities, incontinence, and urinary retention.

Paradoxical reactions such as stimulation, agitation, rage, increased muscle spasticity, sleep disturbances, and hallucinations may occur. Should these occur, discontinue the drug.

During prolonged treatment, periodic blood counts, urinalysis, and blood chemistry analysis are advisable. Minor EEG changes, of unknown significance, have been observed.

Liver enzyme elevations, gynecomastia and galactorrhea have been reported but no causal relationship was established.

DRUG ABUSE AND DEPENDENCE
Physical and Psychological Dependence: Withdrawal symptoms including seizures have occurred following abrupt discontinuance or rapid dose reduction of benzodiazepines. (See Warnings). Dosage should be gradually tapered under close supervision. Patients with a history of seizures or epilepsy should not be abruptly withdrawn from XANAX. Addiction-prone individuals should be under careful surveillance. *Controlled Substance Class*: XANAX is a controlled substance and has been assigned to schedule IV.

OVERDOSAGE
Manifestations include somnolence, confusion, impaired coordination, diminished reflexes and coma. No delayed reactions have been reported.

DOSAGE AND ADMINISTRATION
Dosage should be individualized.

The usual starting dose is 0.25 to 0.5 mg, t.i.d. Maximum total daily dose is 4 mg. In the elderly or debilitated, the usual starting dose is 0.25 mg, two or three times daily. Reduce dosage gradually when terminating therapy, by no more than 0.5 mg every three days.

HOW SUPPLIED
XANAX Tablets are available as 0.25 mg, 0.5 mg, and 1 mg tablets.

CAUTION:
FEDERAL LAW PROHIBITS DISPENSING WITHOUT PRESCRIPTION. B-7-S

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★ **Affiliated Clinical Investigation Societies: the Western Association of Physicians; the Western Society for Clinical Investigation; the Western Section, American Federation for Clinical Research; the Western Society for Pediatric Research; the Western Region, Society for Investigative Dermatology.**

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ARIZONA

The following list of continuing medical education programs in Arizona is compiled by the Arizona Medical Association. All courses listed have been certified as meeting the criteria for Category I of the ArMA CME Certificate and the AMA Physicians Recognition Award. To list Category I continuing medical education programs, please send information to Arizona Medical Association, 810 West Bethany Home Road, Phoenix, AZ 85013; or phone (602) 246-8901.

Brochures and registration forms are available from the contact person or organization sponsoring the program.

July 29-30—**Coconino County Medical Society's Summer Medical Seminar.** Little America Hotel, Flagstaff. Fri-Sat. Contact: Coconino County Medical Society, (602) 774-1886.

October 21-23—**Diagnosis and Management of Respiratory Diseases.** The Boulders, Scottsdale. Fri-Sun. Contact: Medical Education Resources, 1 (800) 421-3756.

November 11-13—**17th Annual Seminar—Musculoskeletal Radiology.** Marriott's Camelback Inn, Scottsdale. Fri-Sun. Contact: Alex Newman, MD, Department of Radiology, Maricopa Medical Center, (602) 267-5361.

CONTACT INFORMATION

ArMA—Contact: Arizona Medical Association, 810 W. Bethany Home Rd, Phoenix, AZ 85013. (602) 246-8901.

U of A—Contact: University of Arizona College of Medicine, Arizona Health Sciences Center, Tucson, AZ 85724. (602) 626-6707.

CALIFORNIA, HAWAII AND NEVADA

This listing of continuing education programs in California, Hawaii and Nevada is supplied by the Committee on Continuing Medical Education of the California Medical Association. All courses and meetings listed have been approved for Category I credit toward the CMA Certificate in Continuing Medical Education. To have accredited courses listed here, please send information at least two months in advance to Department of Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690; or phone (415) 863-5522. For a list of organizations approved for Category I credit toward the CMA Certificate in Continuing Medical Education or for more information on accreditation or certification, please write to the above address.

ALLERGY

October 14—**18th Course on Allergy and Immunology.** Pacific Presbyterian Medical Center at San Francisco. Fri. Contact: Herbert S. Kaufman, MD, PPMC, 2340 Clay St, Rm 313, San Francisco 94115. (415) 923-3441.

ANESTHESIOLOGY

June 16-19—**California Society of Anesthesiologists 1988 Annual Meeting** at Marriott Hotel, Anaheim. Thurs-Sun. 16 hrs. $150-225. Contact: California Society of Anesthesiologists, 1065 Hillsdale Blvd, #410, Foster City 94404. (415) 345-3020.

August 21-27—**Hawaiian Seminar on Clinical Anesthesia.** California Society of Anesthesiologists at Inter-Continental Hotel, Wailea, Maui. Sun-Sat. 20 hrs. $325/$375. Contact: CSA, 1065 E. Hilldale Blvd, Ste 410, Foster City 94404. (415) 345-3020.

September 30-October 1—**Anesthesia Practice 1988.** Anesthesiology Educational Foundation. Fri-Sun. 11 hrs. Contact: AEF, PO Box 24230, Federal Building, Los Angeles 90024. (213) 825-0736.

October 16-21—**Hawaiian Seminar on Clinical Anesthesia.** California Society of Anesthesiologists at Westin Maui Hotel, Maui. Sun-Fri. 20 hrs. $325/$375. Contact: CSA, 1065 Hilldale Blvd, Ste 410, Foster City 94404. (415) 345-3020.

CARDIOLOGY

June 23-25—**Consultative Cardiology: Update in Diagnostic and Therapeutic Techniques.** American College of Cardiology at Newporter Resort, Newport Beach. Thurs-Sat. 14 hrs. $350. Contact: Extramural Programs Dept, ACC, 9111 Old Georgetown Rd, Bethesda, MD 20814. (800) 253-4636.

June 24-25—**Cardiovascular Drug Therapy II.** USC at Century Plaza Hotel, Century City. Fri-Sat. 12 hrs. $110. Contact: USC.

June 30-July 2—**Consultative Cardiology: Update in Diagnostic and Therapeutic Techniques.** ACC, Orange Coast Heart Institute and Hoag Memorial Hospital at Westin South Coast Plaza, Costa Mesa. Thur-Sat. Contact: Registration Secretary, EP Dept., ACC, 9111 Old Georgetown Rd, Bethesda, MD 20814.

July 22-23—**Arrhythmias: Interpretation, Diagnosis and Management.** Medical Education Resources at Disneyland Hotel, Anaheim. Fri-Sat. $295. Contact: Deborah Wilderson, MER, 5808 S. Rapp St, Ste 202, Littleton, CO 80120. (800) 421-3756.

August 4-6—**Critical Care Cardiology.** American College of Cardiology at Fairmont Hotel, San Francisco. Thurs-Sat. 17 hrs. $375. Contact: ACC Extramural Programs, Dept 5080, Washington, DC 20061-5080. (800) 253-4636.

KEY TO ABBREVIATIONS

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690. (415) 863-5522.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Herbert M. Thomas, MD, MPH, Director of CME, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th Street, Los Angeles 90059. (213) 603-3183.

LLU: Loma Linda University
Contact: James J. Couperus, MD, Associate Dean for Educational Affairs, Loma Linda University School of Medicine, Loma Linda 92350.

PMC: Pacific Medical Center
Contact: Continuing Education, Pacific Medical Center, PO Box 7999, San Francisco 94120. (415) 563-4321, ext 2761.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Medical School Office Building, Suite X-365, Stanford 94305-6114. (415) 723-5594.

UCD: University of California, Davis
Contact: Ruth Feryok, Director, Office of Continuing Medical Education, University of California, Davis, School of Medicine, 2701 Stockton Boulevard, Sacramento 95817. (916) 453-5390.

UCI: University of California, Irvine
Contact: Melvin I. Marks, MD, Assistant Dean, University of California, Irvine, California College of Medicine, c/o UCI/CME Program, Memorial Medical Center, 2801 Atlantic Avenue, Long Beach 90801-1428. (213) 595-3811, or (714) 856-5414, UCI Extension.

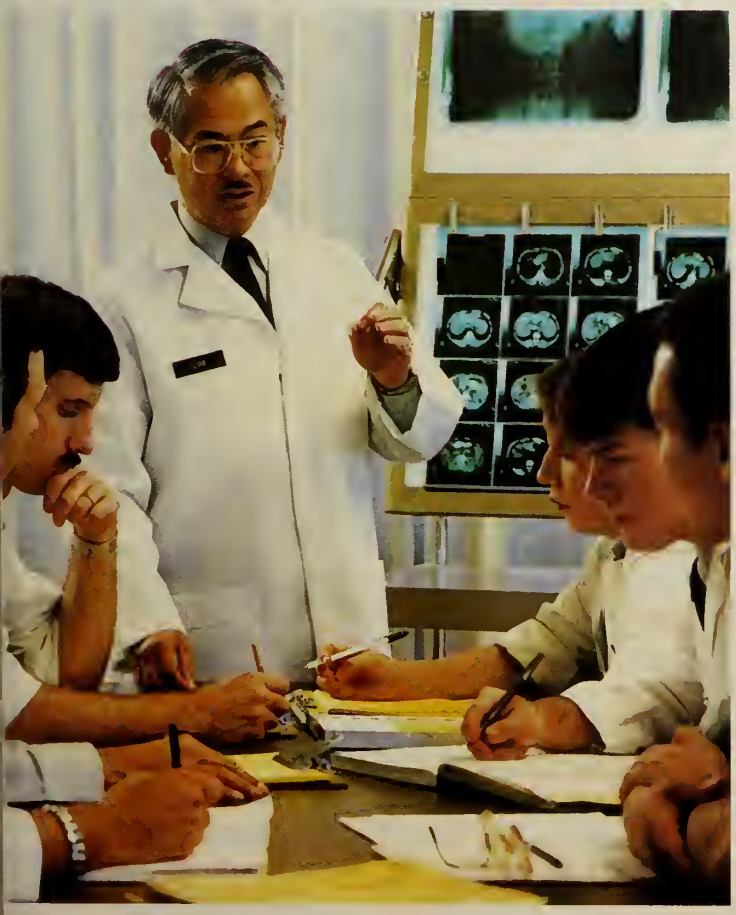
UCLA: University of California, Los Angeles
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, PO Box 24902, UCLA, Los Angeles 90024. (213) 825-7241.

UCSD: University of California, San Diego
Contact: Office of Continuing Medical Education, University of California, San Diego, School of Medicine (M-017), La Jolla 92093. (619) 534-3713.

UCSF: University of California, San Francisco
Contact: Robert Maggio, Administrative Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 476-4251.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 1975 Zonal Ave, KAM314, Los Angeles 90033. (213) 224-7051.

(Continued on Page 638)



ROBERT CHEONG LIM, J.R., M.D.

Professor of Surgery, University of California School of Medicine, San Francisco, California

Chief, Vascular Surgery Service, San Francisco General Hospital

Consultant, Letterman Army Medical Center

Colonel, U.S. Army Reserve

EDUCATION University of California at Berkeley, A.B.; University of California School of Medicine, San Francisco, M.D.

RESIDENCY University of California School of Medicine.

FELLOWSHIPS NIH Fellowship in Vascular Surgery, V.A. Hospital, San Francisco; National Heart Institute Special Fellowship in Thromboembolic Diseases and Microcirculation, University of Gothenburg, Sweden.

OUTSTANDING ACHIEVEMENTS Joe Shoong Fellowship; Earl Hamilton Cornell Scholarship in Medicine; Ligature Order (Sweden); Alpha Omega Alpha; Distinguished Service Award, Youth Opportunity Program, HEW; Special Consultant, Special Project Office on Emergency Medical Services, HEW; Chinese-American Physicians Society; Who's Who in America.

"My professional career is devoted to patient care, teaching and research. Because of my special interest in the field of trauma surgery, I feel especially close to the work being done at Army medical centers such as Letterman Army Medical Center in San Francisco. I am particularly impressed with what they are doing to prepare young Army surgeons in dealing with trauma injuries.

"I joined the Army Reserve because I personally wanted to become more involved with military medicine at Letterman. It has a superior training program, and the quality of military medicine practiced is outstanding. The excellent care patients receive at Army medical facilities is up-to-date and surpasses the standard of care in many means. By being part of that team, I can provide the necessary backup, if needed, in a national emergency.

"The opportunities in the Army Reserve are really far-reaching, especially for doctors in resident training. One, it provides opportunities to augment their training and broaden their exposure. Two, they will get additional compensation. And three, it gives them a preview of military medicine for a possible career choice after residency."

Find out more about the medical opportunities in the Army Reserve. Call toll free: 1-800-USA-ARMY.

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CONTINUING MEDICAL EDUCATION

(Continued from Page 636)

October 21-22—**Arrhythmias: Interpretation, Diagnosis and Management.** Medical Education Resources at Hyatt on Union Square, San Francisco. Fri-Sat. $295. Contact: Deborah Wilderson, MER, 5808 S. Rapp St, Ste 202, Littleton, CO 80120. (800) 421-3756.

DERMATOLOGY

August 12-14—**Dermatologic Surgery: State of the Art 1988.** Stanford University at Monterey Sheraton, Monterey. Fri-Sun. Contact: Paul H. Jacobs, MD, Dept. of Dermatology, UMC Stanford, 94305. (415) 723-6105.

August 21-28—**International Symposium: Hot Spots in Dermatology.** Kauai Medical Group at Molokai, Hawaii. One week. Contact: David Elpern, MD, 3420-B Kuhio Highway, Lihue, Hawaii 96766. (808) 245-1507.

EMERGENCY MEDICINE

June 20-24—**Postgraduate Institute for Emergency and Primary Care Physicians, Symposium III & Optional Advanced Emergency Procedures Laboratory.** UCSD at Hanalei Hotel, Hawaii. Mon-Fri. 32 hrs. $450. Contact: UCSD.

July 22-24—**Advanced Cardiac Life Support.** CPR Seminars at Ralph K. Davies Medical Center, San Francisco. Fri-Sun. Contact: CPR Seminars, 833 Market St, Ste 421, San Francisco 94103. (415) 543-7282.

August 22-26—**Postgraduate Institute for Emergency and Primary Care Physicians, Symposium II & Optional Advanced Emergency Procedures Laboratory.** UCSD. Mon-Fri. 32 hrs. $450. Contact: UCSD.

August 29-September 2—**Topics in Emergency Medicine.** UCSF at Holiday Inn Union Square, San Francisco. Mon-Fri. 31 hrs. $420. Contact: UCSF.

October 10-14—**Postgraduate Institute for Emergency and Primary Care Physicians, Symposium I & Optional Advanced Emergency Procedures Laboratory.** UCSD at Catamaran Resort Hotel, San Diego. Mon-Fri. 32 hrs. $450. Contact: UCSD.

October 21-23—**Advanced Cardiac Life Support.** CPR Seminars at Ralph K. Davies Medical Center, San Francisco. Fri-Sun. Contact: CPR Seminars, 833 Market St, Ste 421, San Francisco 94103. (415) 543-7282.

November 4-6—**Management of the Child With Head Injury.** Children's Hospital Oakland at Monterey Conference Center and Hotel Pacific, Monterey. Fri-Sun. 12 hrs. $280. Contact: Kim Leadon, Continuing Medical Education, Children's Hospital Oakland, 747-52nd St, Oakland 94609. (415) 428-3021.

November 14-18—**Postgraduate Institute for Emergency and Primary Care Physicians, Symposium III & Optional Advanced Emergency Procedures Laboratory.** UCSD at Hanalei Hotel, Hawaii. Mon-Fri. 32 hrs. $450. Contact: UCSD.

December 5-9—**Postgraduate Institute for Emergency and Primary Care Physicians, Symposium II & Optional Advanced Emergency Procedures Laboratory.** UCSD. Mon-Fri. 32 hrs. $450. Contact: UCSD.

INTERNAL MEDICINE

June 20-24—**Advances in Internal Medicine.** UCSF at San Francisco. Mon-Fri. 32 hrs. $485. Contact: UCSF.

August 1-5—**Internal Medicine—36th Annual Update and Board Review.** USC at Health Sciences Campus, Los Angeles. Mon-Fri. 38 hrs. $295. Contact: USC.

September 15-18—**Medical Acupuncture for Physicians: Part I.** UCLA at Bay View Plaza Holiday Inn, Santa Monica. Thurs-Sun. 200 hrs. $3,200. Contact: UCLA.

September 22-24—**International Symposium on Medical Virology.** UCI at Ramada Renaissance Hotel, San Francisco. Thurs-Sat. Contact: Dr Luis M. de la Maza, Department of Pathology, Rt 84, UCI Medical Center, 101 City Drive S., Orange, 92668. (714) 634-6868.

October 4-7—**Rheumatology and Clinical Immunology.** UCSF at Stanford Court, San Francisco. Tues-Fri. 19 hrs. $395. Contact: UCLA.

November 3-5—**New Directions in Anti-viral Chemotherapy.** UCSF at Hyatt on Union Square, San Francisco. Thurs-Sat. $100. Contact: UCSF.

November 7-9—**12th Annual Cancer Symposium.** Scripps Memorial Cancer Hospital at Sheraton Harbor Island Hotel E, San Diego. Mon-Wed. 21 hrs. $390. Contact: Nomi Feldman, Conference Coordinator, 3770 Tansy St, San Diego 92121. (619) 453-6222.

December 30-January 8—**Medical Acupuncture for Physicians: Part II.** UCLA at Bay View Plaza Holiday Inn, Santa Monica. 10 days. 200 hrs. $3,200. Contact: UCLA.

OB/GYN

June 29-July 4—**6th Annual Controversies in Obstetrics and Gynecology.** Center for Health Education at Mauna Kea Beach Hotel, Kamuela, Hawaii. Thurs-Sun. 24 hrs. $600. Contact: Center for Health Education, 2081 Atlantic Ave, PO Box 1428, Long Beach 90801. (213) 595-3811.

June 30-July 3—**6th Annual Controversies in Obstetrics & Gynecology.** Center for Health Education at Mauna Kea Beach Hotel, Hawaii. Thur-Sun. Contact: The Center for Health Education, 2081 Atlantic Ave., PO Box 1428, Long Beach, 90801-1428. (213) 595-3811.

August 19-21—**1988—Office Gynecology for the Primary Care Physician.** Continuing Medical Education Associates and San Diego State University at Hyatt Islandia, San Diego. Fri-Sun. 18 hrs. $295. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

November 10-13—**Current Issues in Perinatal Medicine.** UCI at Marriott's Rancho Las Palmas Resort, Palm Springs. Thurs-Sat. Contact: UCI.

November 12—**Infertility Update V.** Scripps Clinic and Research Foundation Amphitheater, La Jolla. Sat. 7 hrs. $110. Contact: Bonny Mower, Box 400S, Dept of Academic Affairs, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 457-8556.

November 13-19—**11th Annual Review Course in Clinical Obstetrics & Gynecology.** The Center for Health Education at Westin South Coast Plaza Hotel, Costa Mesa. Sun-Sat. Contact: The Center for Health Education, 2081 Atlantic Ave., PO Box 1428, Long Beach, 90801-1428. (213) 595-3811.

PEDIATRICS

June 24-25—**Current Concepts in Child Neurology 1988.** Children's Hospital San Diego at the Holiday Inn Montgomery Field, San Diego. Fri-Sat. 10 hrs. Contact: Continuing Medical Education Office, Children's Hospital. (619) 576-4072.

August 22-24—**Pediatrics Update: 1988.** San Diego State University at Hyatt Islandia, San Diego. Mon-Wed. 18 hrs. $295. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

October 15-20—**American Academy of Pediatrics Annual Session.** AAP. Sat-Thurs. Contact: AAP, 1801 Hinman Ave., Evanston, IL 60201.

October 22-29—**13th Annual Pediatrics for the Practitioner: A Pediatric Symposium.** Center for Health Education at Mauna Kea Beach Hotel, Hawaii. One week. Contact: The Center for Health Education, PO Box 1428, Long Beach 90801-1428.

PSYCHIATRY

November 18-20—**34th Annual Group Therapy Symposium.** UCSF. Fri-Sun. Contact: UCSF.

RADIOLOGY

July 16-17—**Two-Day Seminar in Breast Imaging with Interpretive Workshops.** Los Angeles Radiological Society at Registry Hotel, Universal City. Sat-Sun. 10 hrs. $200. Contact: LARS, PO Box 91215, Los Angeles 90009-1215. (213) 642-0921.

July 28-31—**Second Annual Symposium on Magnetic Resonance Imaging.** Hoag Memorial Hospital at Ritz-Carleton Hotel, Laguna Niguel. Thurs-Sun. $395. Contact: Mary J. Ryals and Associates, PO Box 920113, Norcross, GA 30092-0113. (404) 641-9773.

August 1-5—**Modern Radiology Practice.** UCSD at Fess Parker Red Lion Resort, Santa Barbara. Mon-Fri. 30 hrs. $425. Contact: Mary J. Ryals and Associates, PO Box 920113, Norcross, GA 30092-0113. (404) 641-9773.

August 22-26—**Radiology: 1988 USC Radiology Summer Hawaiian Seminar.** USC at Kauai Westin, Lihue, Hawaii. Mon-Fri. 28 hrs. $475. Contact: USC.

August 25-28—**Fourth Annual Physics and Biology of Radiology.** UCSD at La Jolla Village Inn. Thurs-Sat. 25 hrs. $395. Contact: Mary J. Ryals and Associates, PO Box 920113, Norcross, GA 30092-0113. (404) 641-9773.

(Continued on Page 639)

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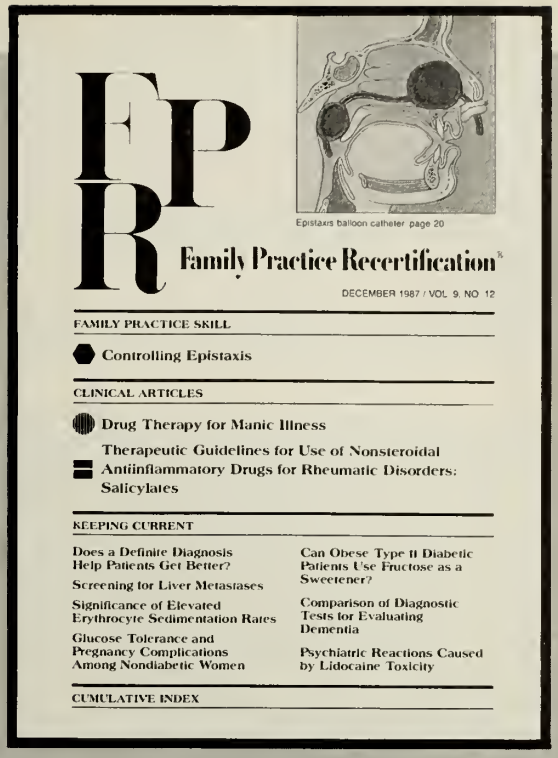
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CONTINUING MEDICAL EDUCATION

(Continued from Page 638)

September 9-11—**Fourth Annual Sonography Update and Review Course.** UCSD at Hanalei Hotel, San Diego. Fri-Sun. 17 hrs. $375. Contact: Mary J. Ryals and Associates, PO Box 920113, Norcross, GA 30092-0113. (404) 641-9773.

October 31-November 1—**San Diego Postgraduate Radiology Course.** UCSD at Hotel del Coronada, San Diego. Mon-Tues. 28 hrs. $450. Contact: UCSD.

December 9-11—**Advanced Seminars in Diagnostic Imaging.** UCSD at Ritz-Carlton, Laguna Niguel. Fri-Sun. 18 hrs. $395. Contact: Dawne Ryals, PO Box 920113, Norcross, GA 30092-0113. (404) 641-9773.

SURGERY

June 20-23—**First International Symposium on Orbital Plastic Surgery.** Plastic Surgery Education Foundation at Westin St Francis Hotel, San Francisco. Mon-Thurs. 25 hrs. $600. Contact: PSEF, 233 N. Michigan Ave, Ste 1900, Chicago, Illinois 60601. (312) 856-1818.

July 30-August 6—**Clinical Problems in External Disease and Anterior Segment Surgery.** USC at Mauna Kea Beach Hotel, Kamuela, Hawaii. 1 week. 26 hrs. $535. Contact: USC.

August 18-21—**Discussions of Current Hand Care Concepts.** Plastic Surgery Education Foundation at San Diego. Thurs-Sun. Contact: PSEF, 233 N. Michigan Ave, Suite 1900, Chicago, Illinois 60601.

September 17—**Summary of Clinical Use of Argon, YAG and CO2 Lasers for Cutaneous Lesions.** Palo Alto Medical Foundation at Palo Alto Medical Clinic. Sat. 6 hrs. Contact: Palo Alto Medical Clinic, 300 Homer Ave, Palo Alto 94301. (415) 321-4121.

October 3-7—**6th Annual Comprehensive Review of Vascular Surgery.** UCLA Miramar Sheraton, Santa Monica. Mon-Fri. 32 hrs. $595. Contact: UCLA.

October 12-14—**Hip and Knee Reconstructive Surgery 1988.** UCLA at Sheraton Princeville Hotel, Kauai, Hawaii. Wed-Fri. Contact: UCLA.

October 14-15—**13th Annual Clinical Neurosciences Symposium.** Dominican Neurologic Institute at Chaminade Conference Center, Santa Cruz. Fri-Sat. 11 hrs. $350. Contact: Karen Rickenbach, DNI Dominican Hospital, 1555 Soquel Dr, Santa Cruz 95065. (408) 462-7562.

December 3—**Reider Laser YAG & Argon Laser/Brachytherapy Symposium.** Center for Health Education, Long Beach. Sat. Contact: Center for Health Education, 2801 Atlantic Ave, PO Box 1428, Long Beach 90801-1428. (213) 595-3811.

December 3—**Summary of Clinical Use of Argon, YAG and CO2 Lasers for Cutaneous Lesions.** Palo Alto Medical Foundation at Palo Alto Medical Clinic. Sat. 6 hrs. Contact: Palo Alto Medical Clinic, 300 Homer Ave, Palo Alto 94301. (415) 321-4121.

OF INTEREST TO ALL PHYSICIANS

June 18-19—**Skills Workshop: Flexible Sigmoidoscopy and Colposcopy.** UCI at Sheraton Newport, Newport Beach. Sat-Sun. 16 hrs. $140-ea., $250-both. Contact: UCI.

June 22-24—**A Journey to Clarity: Symposium for the Exploration and Integration of the Issues in the Recovery Process.** Monterey Community Hospital at Monterey Conference Center. Wed-Fri. $250. Contact: Nomi Feldman, Conference Coordinator, 3770 Tansy St, San Diego 92121. (619) 453-6222.

June 24-26—**Family Practice Intensive Refresher.** USC at Pasadena Hilton Hotel. Fri-Sun. 16 hrs. $250. Contact: USC.

June 25-26—**10th Annual Poison Control Center Symposium on Toxicology and Poisoning.** UCSF and Continuing Medical Education in Pharmacy at San Francisco. Sat-Sun. 14 hrs. $235. Contact: Continuing Education S/P, UCSF, Box 0446, San Francisco 94143. (415) 476-4194.

(Continued on Page 646)

Now on Medi-Cal

The One for an Important Spectrum of Patient Benefits

Just one tablet once a day in duodenal ulcer

PEPCID® (Famotidine, MSD) is contraindicated in patients who are hypersensitive to any component of this medication.

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Now Available on Medi-Cal May 1, 1988

PROMPT PAIN RELIEF

Begins on day 1, lasts all night and all day in most patients.

RAPID ULCER HEALING

Healing often complete by week 4.

EXCELLENT TOLERABILITY

Generally well tolerated—adverse reaction incidence comparable to placebo in clinical studies.

SIMPLIFIED DOSAGE

One 40-mg tablet h.s. for acute therapy in active duodenal ulcer.

One 20-mg tablet h.s. for maintenance therapy in duodenal ulcer.

Dosing intervals may need to be prolonged or dosage reduced in patients with severe renal insufficiency (creatinine clearance <10 mL/min).

Medi-Cal Approval Numbers

1758 F	1758 D
40-mg tablet	20-mg tablet

COST-EFFECTIVE THERAPY

Cost per month of therapy less than Zantac.*,**

*registered trademark of Glaxo Group Limited.
**Based on the manufacturer's direct or wholesale price to the retail pharmacist.

TABLETS, 20 mg and 40 mg

Pepcid® ONCE A DAY

(Famotidine/MSD)

MSD
MERCK SHARP & DOHME

For a Brief Summary of Prescribing Information, please see following page.

TABLETS
Pepcid®
(Famotidine/MSD)
20 mg and 40 mg

ORAL SUSPENSION
Pepcid®
(Famotidine for Oral Suspension/MSD)
40 mg per 5 mL

INJECTION
Pepcid® IV
(Famotidine/MSD)
20 mg per 2 mL

Contraindications: Hypersensitivity to any component.

Precautions: ***General:*** Symptomatic response to therapy does not preclude the presence of gastric malignancy.

Patients with Severe Renal Insufficiency: Longer intervals between doses or lower doses may be needed in patients with severe renal insufficiency (creatinine clearance <10 mL/min) to adjust for the longer elimination half-life of famotidine (see Clinical Pharmacology and Dosage and Administration sections of Prescribing Information).

Information for Patients: The oral suspension should be shaken vigorously for 5-10 seconds prior to each use, and unused constituted oral suspension should be discarded after 30 days.

Drug Interactions: No drug interactions have been identified. Compounds tested in man include warfarin, theophylline, phenytoin, diazepam, aminopyrine, and antipyrine.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In rats and mice given oral doses up to approximately 2500 times the recommended human dose for active duodenal ulcer, there was no evidence of carcinogenic potential, no evidence of a mutagenic effect, and fertility and reproductive performance were not affected.

Pregnancy: *Pregnancy Category B*—There are no adequate or well-controlled studies in pregnant women. Use during pregnancy only if clearly needed.

Nursing Mothers: It is not known whether famotidine is secreted into human milk; however, it is secreted into the milk of lactating rats. A decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness in children have not been established.

Use in Elderly Patients: No dosage adjustment is required based on age but may be necessary in severe renal impairment (see Clinical Pharmacology section of Prescribing Information).

Adverse Reactions: The adverse reactions listed below have been reported during domestic and international clinical trials in approximately 2500 patients. In the placebo-controlled clinical trials, the incidence of adverse experiences with PEPCID Tablets, 40 mg at bedtime, was similar to that with placebo.

Incidence Greater than 1%: The following adverse reactions have been reported to occur in more than 1% of patients on therapy with PEPCID in controlled clinical trials and may be causally related to the drug: headache (4.7%), dizziness (1.3%), constipation (1.2%), and diarrhea (1.7%).

Causal Relationship Unknown: The following other adverse reactions have been reported in clinical trials. While a causal relationship could not be established for these infrequently reported events, causality cannot be excluded. *Body as a Whole*—Fever, asthenia, fatigue. *Cardiovascular*—Palpitations. *Gastrointestinal*—Nausea, vomiting, abdominal discomfort, anorexia, dry mouth, liver enzyme abnormalities. *Hematologic*—Thrombocytopenia. *Hypersensitivity*—Orbital edema, conjunctival injection. *Musculoskeletal*—Musculoskeletal pain, arthralgia. *Nervous System/Psychiatric*—Paresthesias; grand mal seizures (single report); psychic disturbances including depression, anxiety, decreased libido, hallucinations (single report); insomnia; somnolence. *Respiratory*—Bronchospasm. *Skin*—Alopecia, acne, pruritus, rash, dry skin, flushing. *Special Senses*—Tinnitus, taste disorder.

The adverse reactions reported for PEPCID Tablets may also occur with PEPCID Oral Suspension or PEPCID I.V.; in addition, transient irritation at the injection site has been observed with PEPCID I.V.

Management of Overdosage: There is no experience to date with deliberate overdosage. Up to 640 mg/day have been given to patients with pathological hypersecretory conditions with no serious adverse effects. In the event of overdosage, treatment should be symptomatic and supportive. Unabsorbed material should be removed from the gastrointestinal tract, the patient should be monitored, and supportive therapy should be employed.

Dosage and Administration: ***Duodenal Ulcer:*** The recommended adult oral dosage for active duodenal ulcer is 40 mg h.s.; most patients heal within 4 weeks, and it is rarely necessary to use the full dosage for longer than 6 to 8 weeks. A regimen of 20 mg b.i.d. is also effective. For maintenance therapy, the recommended oral dosage is 20 mg h.s.

Pathological Hypersecretory Conditions (e.g., Zollinger-Ellison Syndrome, Multiple Endocrine Adenomas): The dosage varies with the individual patient; the recommended adult oral starting dosage is 20 mg q6h, but some patients may require a higher starting dosage. Dosages should be adjusted to individual patient needs and continued as long as clinically indicated; up to 160 mg q6h have been administered to some patients with severe Zollinger-Ellison syndrome.

Oral Suspension: The Oral Suspension may be substituted for Tablets for those patients who cannot swallow tablets.

Directions for Preparing PEPCID Oral Suspension: Prepare suspension at time of dispensing. Slowly add 46 mL Purified Water. Shake vigorously for 5-10 seconds immediately after adding the water and immediately before use.

Stability of PEPCID Oral Suspension: Unused constituted oral suspension should be discarded after 30 days.

Intravenous Administration: In some hospitalized patients with pathological hypersecretory conditions or intractable ulcers, or in patients who are unable to take oral medication, the recommended intravenous dosage is 20 mg q12h. For preparation of solutions for injection or infusion and for compatible diluents, please see Prescribing Information. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

Concomitant Use of Antacids: Antacids may be given concomitantly if needed.

Dosage Adjustment for Patients with Severe Renal Insufficiency: In patients with severe renal insufficiency (creatinine clearance less than 10 mL/min), the elimination half-life of famotidine may exceed 20 hours, reaching approximately 24 hours in anuric patients. Although no relationship of adverse effects to high plasma levels has been established, to avoid excess accumulation of the drug, the dosage may be reduced to 20 mg h.s. or the dosing interval may be prolonged to 36 to 48 hours as indicated by the patient's clinical response.

How Supplied: Tablets, containing 20 mg or 40 mg famotidine, with hydroxypropyl cellulose, hydroxypropyl methylcellulose, iron oxides, magnesium stearate, microcrystalline cellulose, starch, talc, and titanium dioxide as inactive ingredients, in bottles of 30 and unit-dose packages of 100; Oral Suspension, containing per 5 mL after constitution with 46 mL Purified Water, 40 mg famotidine, with citric acid, flavors, microcrystalline cellulose and carboxymethylcellulose sodium, sucrose, and xanthan gum as inactive ingredients, and sodium benzoate 0.1%, sodium methylparaben 0.1%, and sodium propylparaben 0.02% added as preservatives, in bottles of 400 mg famotidine for constitution; Solution for intravenous injection, containing 10 mg famotidine per mL, with L-aspartic acid 4 mg, mannitol 20 mg, and water for injection q.s. 1 mL as inactive ingredients, and benzyl alcohol 0.9% added as preservative to the multidose vial, as 10x2-mL single-dose vials and as 4-mL vials.

For more detailed information, consult your MSD Representative or see Prescribing Information.
Merck Sharp & Dohme, Division of Merck & Co., Inc., West Point, PA 19486

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MERCK SHARP & DOHME

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The World's Most Popular K*

Slow-K®

potassium chloride
slow-release tablets
8 mEq (600 mg)

It means "dependability" in almost any language

*Based on worldwide sales data on file, CIBA Pharmaceutical Company.
Capsule or tablet slow-release potassium chloride preparations should be reserved for patients who cannot tolerate, refuse to take, or have compliance problems with liquid or effervescent potassium preparations because of reports of intestinal and gastric ulceration and bleeding with slow-release KCl preparations.

Before prescribing, please consult Brief Prescribing Information on next page.

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C I B A

128-3568-A

The World's Most Popular K

For good reasons

- ☐ **It works**—a 12-year record of efficacy[1]
- ☐ **It's safe**—unsurpassed by any other KCl tablet or capsule[2]*
- ☐ **It's acceptable vs liquids**—greater palatability, fewer GI complaints, lower incidence of nausea[2]
- ☐ **It's comparable to 10 mEq**—in low-dosage supplementation[3]†
- ☐ **It's economical**—less expensive than all other leading KCl slow-release supplements on a per tablet cost to the patient[1]

Slow-K®
potassium chloride
slow-release tablets 8 mEq (600 mg)

For patients who can't or won't tolerate liquid KCl.

*The most common adverse reactions to potassium salts are gastrointestinal side effects.

†Pooled mean serum potassium following oral administration of 30 mEq K-Tab compared to 24 mEq Slow-K in diuretic-treated hypertensives (n = 20) over 8 weeks.

C I B A

References: 1. Data on file, CIBA Pharmaceutical Company. 2. Skoutakis VA, Acchiardo SR, Wojciechowski NJ, et al: Liquid and solid potassium chloride Bioavailability and safety *Pharmacotherapy* 1980;4(6):392-397. 3. Skoutakis VA, Carter CA, Acchiardo SR. Therapeutic assessment of Slow-K and K-Tab potassium chloride formulations in hypertensive patients treated with thiazide diuretics *Drug Intell Clin Pharm* 1987;21:436-440.

Slow-K*
potassium chloride USP
Slow-Release Tablets
8 mEq (600 mg)

BRIEF SUMMARY (FOR FULL PRESCRIBING INFORMATION SEE PACKAGE INSERT)

INDICATIDNS AND USAGE

BECAUSE OF REPDRTS DF INTESTINAL AND GASTRIC ULCERATION AND BLEEDING WITH SLOW-RELEASE PDTASSIUM CHLORIDE PREPARATIONS, THESE DRUGS SHOULD BE RESERVED FOR THDSE PATIENTS WHO CANNOT TOLERATE OR REFUSE TO TAKE LIQUID DR EFFERVESCENT POTASSIUM PREPARATIONS OR FOR PATIENTS IN WHOM THERE IS A PROBLEM OF COMPLIANCE WITH THESE PREPARATIONS.

1. For therapeutic use in patients with hypokalemia with or without metabolic alkalosis; in digitalis intoxication and in patients with hypokalemic familial periodic paralysis.

2. For prevention of potassium depletion when the dietary intake of potassium is inadequate in the following conditions: patients receiving digitalis and diuretics for congestive heart failure, hepatic cirrhosis with ascites; states of aldosterone excess with normal renal function; potassium-losing nephropathy; and certain diarrheal states

3. The use of potassium salts in patients receiving diuretics for uncomplicated essential hypertension is often unnecessary when such patients have a normal dietary pattern. Serum potassium should be checked periodically, however, and if hypokalemia occurs, dietary supplementation with potassium-containing foods may be adequate to control milder cases. In more severe cases supplementation with potassium salts may be indicated

CONTRAINDICATIONS

Potassium supplements are contraindicated in patients with hyperkalemia, since a further increase in serum potassium concentration in such patients can produce cardiac arrest. Hyperkalemia may complicate any of the following conditions: chronic renal failure, systemic acidosis such as diabetic acidosis, acute dehydration, extensive tissue breakdown as in severe burns, adrenal insufficiency, or the administration of a potassium-sparing diuretic (e.g., spironolactone, triamterene) (see OVERDOSAGE).

All solid dosage forms of potassium supplements are contraindicated in any patient in whom there is cause for arrest or delay in tablet passage through the gastrointestinal tract. In these instances, potassium supplementation should be with a liquid preparation. Wax-matrix potassium chloride preparations have produced esophageal ulceration in certain cardiac patients with esophageal compression due to an enlarged left atrium.

WARNINGS

Hyperkalemia (See OVERDOSAGE).

In patients with impaired mechanisms for excreting potassium, the administration of potassium salts can produce hyperkalemia and cardiac arrest. This occurs most commonly in patients given potassium by the intravenous route but may also occur in patients given potassium orally. Potentially fatal hyperkalemia can develop rapidly and be asymptomatic.

The use of potassium salts in patients with chronic renal disease, or any other condition which impairs potassium excretion, requires particularly careful monitoring of the serum potassium concentration and appropriate dosage adjustment.

Interaction With Potassium-Sparing Diuretics

Hypokalemia should not be treated by the concomitant administration of potassium salts and a potassium-sparing diuretic (e.g., spironolactone or triamterene), since the simultaneous administration of these agents can produce severe hyperkalemia.

Gastrointestinal Lesions

Potassium chloride tablets have produced stenotic and or ulcerative lesions of the small bowel and deaths. These lesions are caused by a high localized concentration of potassium ion in the region of a rapidly dissolving tablet, which injures the bowel wall and thereby produces obstruction, hemorrhage, or perforation. Slow-K is a wax-matrix tablet formulated to provide a controlled rate of release of potassium chloride and thus to minimize the possibility of a high local concentration of potassium ion near the bowel wall. While the reported frequency of small-bowel lesions is much less with wax-matrix tablets (less than one per 100,000 patient-years) than with enteric-coated potassium chloride tablets (40-50 per 100,000 patient-years) cases associated with wax-matrix tablets have been reported both in foreign countries and in the United States. In addition, perhaps because the wax-matrix preparations are not enteric-coated and release potassium in the stomach, there have been reports of upper gastrointestinal bleeding associated with these products. The total number of gastrointestinal lesions remains approximately one per 100,000 patient-years. Slow-K should be discontinued immediately and the possibility of bowel obstruction or perforation considered if severe vomiting, abdominal pain, distention, or gastrointestinal bleeding occurs.

Metabolic Acidosis

Hypokalemia in patients with metabolic acidosis should be treated with an alkalinizing potassium salt such as potassium bicarbonate, potassium citrate, or potassium acetate

PRECAUTIONS

General:

The diagnosis of potassium depletion is ordinarily made by demonstrating hypokalemia in a patient with a clinical history suggesting some cause for potassium depletion. In interpreting the serum potassium level, the physician should bear in mind that acute alkalosis *per se* can produce hypokalemia in the absence of a deficit in total body potassium, while acute acidosis *per se* can increase the serum potassium concentration into the normal range even in the presence of a reduced total body potassium

Information for Patients

Physicians should consider reminding the patient of the following

To take each dose without crushing, chewing, or sucking the tablets

To take this medicine only as directed. This is especially important if the patient is also taking both diuretics and digitalis preparations

To check with the physician if there is trouble swallowing tablets or if the tablets seem to stick in the throat.

To check with the doctor at once if tarry stools or other evidence of gastrointestinal bleeding is noticed.

Laboratory Tests

Regular serum potassium determinations are recommended. In addition, during the treatment of potassium depletion, careful attention should be paid to acid-base balance, other serum electrolyte levels, the electrocardiogram, and the clinical status of the patient, particularly in the presence of cardiac disease, renal disease, or acidosis.

Drug Interactions

Potassium-sparing diuretics: see WARNINGS.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term carcinogenicity studies in animals have not been performed.

Pregnancy Category C

Animal reproduction studies have not been conducted with Slow-K. It is also not known whether Slow-K can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Slow-K should be given to a pregnant woman only if clearly needed.

Nursing Mothers

The normal potassium ion content of human milk is about 13 mEq/L. It is not known if Slow-K has an effect on this content. Caution should be exercised when Slow-K is administered to a nursing woman.

Pediatric Use

Safety and effectiveness in children have not been established

ADVERSE REACTIONS

One of the most severe adverse effects is hyperkalemia (see CONTRAINDICATIONS, WARNINGS, and OVERDOSAGE). There also have been reports of upper and lower gastrointestinal conditions including obstruction, bleeding, ulceration, and perforation (see CONTRAINDICATIONS and WARNINGS); other factors known to be associated with such conditions were present in many of these patients.

The most common adverse reactions to oral potassium salts are nausea, vomiting, abdominal discomfort, and diarrhea. These symptoms are due to irritation of the gastrointestinal tract and are best managed by taking the dose with meals or reducing the dose.

Skin rash has been reported rarely.

OVERDOSAGE

The administration of oral potassium salts to persons with normal excretory mechanisms for potassium rarely causes serious hyperkalemia. However, if excretory mechanisms are impaired or if potassium is administered too rapidly intravenously, potentially fatal hyperkalemia can result (see CONTRAINDICATIONS and WARNINGS). It is important to recognize that hyperkalemia is usually asymptomatic and may be manifested only by an increased serum potassium concentration (6.5-8.0 mEq/L) and characteristic electrocardiographic changes (peaking of T waves, loss of P wave, depression of S-T segment, and prolongation of the Q-T interval). Late manifestations include muscle paralysis and cardiovascular collapse from cardiac arrest (9-12 mEq/L).

Treatment measures for hyperkalemia include the following: (1) elimination of foods and medications containing potassium and of potassium-sparing diuretics; (2) intravenous administration of 300-500 ml/hr of 10% dextrose solution containing 10-20 units of insulin per 1,000 ml; (3) correction of acidosis, if present, with intravenous sodium bicarbonate; (4) use of exchange resins, hemodialysis, or peritoneal dialysis.

In treating hyperkalemia in patients who have been stabilized on digitalis, too rapid a lowering of the serum potassium concentration can produce digitalis toxicity

DOSAGE AND ADMINISTRATION

The usual dietary intake of potassium by the average adult is 40-80 mEq per day. Potassium depletion sufficient to cause hypokalemia usually requires the loss of 200 or more mEq of potassium from the total body store. Dosage must be adjusted to the individual needs of each patient but is typically in the range of 20 mEq per day for the prevention of hypokalemia to 40-100 mEq or more per day for the treatment of potassium depletion. Large numbers of tablets should be given in divided doses.

Note: Slow-K slow-release tablets must be swallowed whole and never crushed, chewed, or sucked.

HOW SUPPLIED

Tablets—600 mg of potassium chloride (equivalent to 8 mEq) round, buff colored, sugar-coated (imprinted Slow-K)

Bottles of 100	NDC 0083-0165-30
Bottles of 1000	NDC 0083-0165-40
Consumer Pack—One Unit	
12 Bottles—100 tablets each	NDC 0083-0165-65
Accu-Pak® Unit Dose (Blister pack)	
Box of 100 (strips of 10)	NDC 0083-0165-33

Do not store above 86°F (30°C). Protect from moisture. Protect from light.

Dispense in tight, light-resistant container (USP).

Dist. by:
CIBA Pharmaceutical Company
Division of CIBA-GEIGY Corporation
Summit, New Jersey 07901

C87-31 (Rev 8/87)

C I B A

128-3568-A

In the treatment of chronic anxiety...

A benzodiazepine withdrawal syndrome...

It doesn't have to be the price of efficacy.

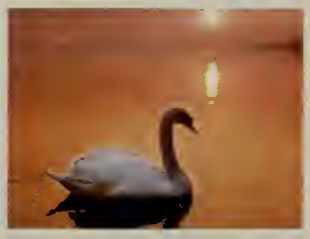
BuSpar relieves anxiety and returns your patient to normal activity without producing a benzodiazepine withdrawal syndrome upon discontinuation[1]
...and without producing significant sedative effects[2] or potentiating the effects of alcohol*[3]

The first choice for chronic anxiety

BuSpar®

Tablets, 5 mg and 10 mg

(buspirone HCl)



for a different kind of calm

*While formal studies of the interaction of BuSpar with alcohol indicate that it does not increase alcohol-induced impairment in motor and mental performance, it is prudent to avoid concomitant use of alcohol and BuSpar.

For Brief Summary, please see following page.

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BuSpar® (buspirone HCl)

References: 1. Lader M. Assessing the potential for buspirone dependence or abuse and effects of its withdrawal. *Am J Med* 1987;82(5A):20-26. 2. Newton RE, *et al.* A review of the side effect profile of buspirone. *Am J Med* 1986;80(3B):17-21. 3. Mattila MJ, *et al.* Acute effects of buspirone and alcohol on psychomotor skills. *J Clin Psychiatry* 1982;43(12,Sec 2):56-60.

Contraindications: Hypersensitivity to buspirone.

Warnings: The administration of BuSpar to a patient taking a monoamine oxidase inhibitor (MAOI) may pose a hazard. Since blood pressure has become elevated when BuSpar was administered concomitantly with an MAOI, such concomitant use is not recommended. BuSpar should not be employed in lieu of appropriate antipsychotic treatment.

Precautions: ***General***—*Interference with cognitive and motor performance.* Although buspirone is less sedating than other anxiolytics and does not produce significant functional impairment, its CNS effects in a given patient may not be predictable, therefore, patients should be cautioned about operating an automobile or using complex machinery until they are reasonably certain that buspirone does not affect them adversely. Although buspirone has not been shown to increase alcohol-induced impairment in motor and mental performance, it is prudent to avoid concomitant use with alcohol.

Potential for withdrawal reactions in sedative/hypnotic/anxiolytic drug dependent patients. Because buspirone will not block the withdrawal syndrome often seen with cessation of therapy with benzodiazepines and other common sedative/hypnotic drugs, before starting buspirone withdraw patients gradually from their prior treatment, especially those who used a CNS depressant chronically. Rebound or withdrawal symptoms may occur over varying time periods, depending in part on the type of drug and its elimination half-life. The withdrawal syndrome can appear as any combination of irritability, anxiety, agitation, insomnia, tremor, abdominal cramps, muscle cramps, vomiting, sweating, flu-like symptoms without fever, and occasionally, even as seizures.

Possible concerns related to buspirone's binding to dopamine receptors. Because buspirone can bind to central dopamine receptors, a question has been raised about its potential to cause acute and chronic changes in dopamine mediated neurological function (e.g., dystonia, pseudoparkinsonism, akathisia, and tardive dyskinesia). Clinical experience in controlled trials has failed to identify any significant neuroleptic-like activity; however, a syndrome of restlessness, appearing shortly after initiation of treatment, has been reported, the syndrome may be due to increased central noradrenergic activity or may be attributable to dopaminergic effects (ie, represent akathisia).

Information for Patients—Patients should be instructed to inform their physician about any medications, prescription or non-prescription, alcohol or drugs they are now taking or plan to take during treatment with buspirone; to inform their physician if they are pregnant, are planning to become pregnant, or become pregnant while taking buspirone; to inform their physician if they are breast feeding; and not to drive a car or operate potentially dangerous machinery until they experience how this medication affects them.

Drug Interactions—Concomitant use with other CNS active drugs should be approached with caution (see **Warnings**). Concomitant use with trazodone may have caused 3- to 6-fold elevations on SGPT (ALT) in a few patients. Buspirone does not displace tightly bound drugs like phenytoin, propranolol, and warfarin from serum proteins, but may displace less firmly bound drugs like digoxin.

Carcinogenesis, Mutagenesis, Impairment of Fertility—No evidence of carcinogenic potential was observed in rats or mice; buspirone did not induce point mutations, nor was DNA damage observed; chromosomal aberrations or abnormalities did not occur.

Pregnancy: Teratogenic Effects—Pregnancy Category B: Should be used during pregnancy only if clearly needed.

Nursing Mothers—Administration to nursing women should be avoided if clinically possible.

Pediatric Use—The safety and effectiveness have not been determined in individuals below 18 years of age.

Use in the Elderly—No unusual, adverse, age-related phenomena have been identified in elderly patients receiving a total, modal daily dose of 15 mg.

Use in Patients with Impaired Hepatic or Renal Function—Since buspirone is metabolized by the liver and excreted by the kidneys, it is not recommended in severe hepatic or renal impairment.

Adverse Reactions (See also Precautions): ***Commonly Observed***—The more commonly observed untoward events include dizziness, nausea, headache, nervousness, lightheadedness, and excitement.

Associated with Discontinuation of Treatment—The more common events causing discontinuation included: central nervous system disturbances (3.4%), primarily dizziness, insomnia, nervousness, drowsiness, lightheaded feeling; gastrointestinal disturbances (1.2%), primarily nausea, miscellaneous disturbances (1.1%), primarily headache and fatigue. In addition, 3.4% of patients had multiple complaints, none of which could be characterized as primary.

Incidence in Controlled Clinical Trials—Adverse events reported by 1% or more of 477 patients who received buspirone in four-week, controlled trials. *Cardiovascular:* Tachycardia/palpitations 1%. *CNS:* Dizziness 12%, drowsiness 10%, nervousness 5%, insomnia 3%, lightheadedness 3%, decreased concentration 2%, excitement 2%, anger/hostility 2%, confusion 2%, depression 2%. *EENT:* Blurred vision 2%. *Gastrointestinal:* Nausea 8%, dry mouth 3%, abdominal/gastric distress 2%, diarrhea 2%, constipation 1%, vomiting 1%. *Musculoskeletal:* Musculoskeletal aches/pains 1%. *Neurological:* Numbness 2%, paresthesia 1%, incoordination 1%, tremor 1%. *Skin:* Skin rash 1%. *Miscellaneous:* Headache 6%, fatigue 4%, weakness 2%, sweating/clamminess 1%.

Other Events Observed During the Entire Pre-marketing Evaluation—The relative frequency of all other undesirable events reasonably associated with the use of buspirone in approximately 3000 subjects who took multiple doses of the drug under well-controlled, open, and uncontrolled conditions is defined as follows: Frequent are those occurring in at least 1/100 patients; infrequent are those occurring in 1/100 to 1/1000 patients, and rare are those occurring in less than 1/1000 patients. *Cardiovascular*—frequent: nonspecific chest pain; infrequent: syncope, hypotension, hypertension; rare: cerebrovascular accident, congestive heart failure, myocardial infarction, cardiomyopathy, bradycardia. *Central Nervous System*—frequent: dream disturbances; infrequent: depersonalization, dysphoria, noise intolerance, euphoria, akathisia, fearfulness, loss of interest, disassociative reaction, hallucinations, suicidal ideation, seizures; rare: feelings of claustrophobia, cold intolerance, stupor, slurred speech, psychosis. *EENT*—frequent: tinnitus, sore throat, nasal congestion; infrequent: redness and itching of the eyes, altered taste, altered smell, conjunctivitis; rare: inner ear abnormality, eye pain, photophobia, pressure on eyes. *Endocrine*—rare: galactorrhea, thyroid abnormality. *Gastrointestinal*—infrequent: flatulence, anorexia, increased appetite, salivation, irritable colon, rectal bleeding; rare: burning of the tongue. *Genitourinary*—infrequent: urinary frequency, urinary hesitancy, menstrual irregularity and spotting, dysuria; rare: amenorrhea, pelvic inflammatory disease, enuresis, nocturia. *Musculoskeletal*—infrequent: muscle cramps, muscle spasms, rigid/stiff muscles, arthralgias. *Neurological*—infrequent: involuntary movements, slowed reaction time; rare: muscle weakness. *Respiratory*—infrequent: hyperventilation, shortness of breath, chest congestion; rare: epistaxis. *Sexual Function*—infrequent: decreased or increased libido; rare: delayed ejaculation, impotence. *Skin*—infrequent: edema, pruritus, flushing, easy bruising, hair loss, dry skin, facial edema, blisters; rare: acne, thinning of nails. *Clinical Laboratory*—infrequent: increases in hepatic aminotransferases (SGOT, SGPT); rare: eosinophilia, leukopenia, thrombocytopenia. *Miscellaneous*—infrequent: weight gain, fever, roaring sensation in the head, weight loss, malaise; rare: alcohol abuse, bleeding disturbance, loss of voice, hiccoughs.

Drug Abuse and Dependence: ***Controlled Substance Class***—Not a controlled substance.

Physical and Psychological Dependence—Buspirone has shown no potential for abuse or diversion and there is no evidence that it causes tolerance, or either physical or psychological dependence. However, since it is difficult to predict from experiments the extent to which a CNS active drug will be misused, diverted, and/or abused once marketed, physicians should carefully evaluate patients for a history of drug abuse and follow such patients closely, observing them for signs of buspirone misuse or abuse (e.g., development of tolerance, incrementation of dose, drug-seeking behavior).

Overdosage: ***Signs and Symptoms***—At doses approaching 375 mg/day the following symptoms were observed: nausea, vomiting, dizziness, drowsiness, miosis, and gastric distress. No deaths have been reported in humans either with deliberate or accidental overdosage.

Recommended Overdose Treatment—General symptomatic and supportive measures should be used along with immediate gastric lavage. No specific antidote is known and dialyzability of buspirone has not been determined.

For complete details, see Prescribing Information or consult your Mead Johnson Pharmaceuticals Representative.

U.S. Patent Nos. 3,717,634 and 4,182,763

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CONTINUING MEDICAL EDUCATION

(Continued from Page 639)

July 1-5—**2nd Annual Family Practice Board Review.** UCSD at Hanalei Hotel, San Diego. Fri-Tues. 25 hrs. $355. Contact: UCSD.

July 5-7—**Family Practice Board Review Course.** UCSF at Cathedral Hill Hotel, San Francisco. Tues-Thurs. 20 hrs. Contact: Program Coordinator, Dept of Family and Community Medicine, 400 Parnassus Ave, A-C9, San Francisco 94143-0900. (415) 476-5250.

July 14-17—**Decentralized Care of People With AIDS: An Educational Seminar for Developmental Approach.** Sonoma County Academic Foundation for Excellence at Flamingo Hotel, Santa Rosa. Thurs-Sun. $275. Contact: Mary Ellen Buechter, SCAFE, 3325 Chanate Rd, Santa Rosa, 95404. (707) 527-4121.

July 15-18—**Caring for People With AIDS and Their Loved Ones.** Concern for Dying: an Educational Council, at Bishop's Ranch, Healdsburg. Fri-Mon. Contact: Penny Weingarten, 250 West 57th St., Room 831, New York, NY 10107. (800) 248-2122.

July 16-18—**Laboratory and Clinical Aspects of Microbiological Diagnosis.** UCLA at Hotel Le Meridien, Newport Beach. Sat-Sun. Contact: UCLA.

July 18-21—**12th Annual Selected Topics for Primary Care Physicians.** LLU. Mon-Thurs. Contact: LLU.

July 25-29—**SPORTS MEDICINE 1988: A Practical Approach to Caring for Today's Athletes.** UCSD at San Diego Princess. Mon-Fri. 23 hrs. Contact: UCSD.

July 27-31—**Wilderness Medicine '88.** Wilderness Medical Society at Squaw Valley, Lake Tahoe. Wed-Sun. 22 hrs. Contact: Jackie Silva, Coordinator, Mountain Medical Seminars, PO Box 321, Yreka, 96097. (916) 842-4667.

August 1-3—**4th International ND: YAG Laser Symposium.** International Laser Foundation at Sheraton Universal Hotel, Los Angeles. Mon-Wed. Contact: ILF, 3960 Park Blvd, Ste E, San Diego 92103. (619) 692-9115.

August 3-6—**15th Annual Meeting: The Peruvian American Medical Society** at Westin Bonaventure Hotel, Los Angeles. Wed-Sat. Contact: Hugo Ortiz, MD, Chairman, Scientific Program, 6488 Tamerlane Dr, West Bloomfield, MI 48322.

August 12-14—**Diagnosis and Management of Respiratory Diseases.** Medical Education Resources at Doubletree Inn, Monterey. Fri-Sun. $225. Contact: Deborah Wilderson, MER, 5808 S. Rapp St, Ste 202, Littleton, CO 80120. (800) 421-3756.

August 13-20—**8th Annual Symposium on Fine Needle Aspiration.** UCSF at Kaanapali Beach, Maui. 1 week. 25 hrs. Contact: UCSF.

August 14-24—**31st Anniversary Postgraduate Refresher Course.** USC at Sheraton Waikiki and Westin Kauai, Hawaii. Sun-Wed. 42 hrs. $535. Contact: USC.

August 17-27—**31st Anniversary Postgraduate Refresher Course.** USC at Sheraton Waikiki and Westin Kauai, Hawaii. Wed-Sat. 41 hrs. $535. Contact: USC.

August 18-19—**7th Annual Symposium: General Medicine Update for Practicing Physicians.** Northern Inyo Hospital, Bishop. Thurs-Fri. 10 hrs. Contact: Lynda Schmidt, Northern Inyo Hospital, 105 Pioneer Lane, Bishop 93514. (619) 873-5811.

August 21-31—**31st Anniversary Postgraduate Refresher Course.** USC at Westin Kauai and Mauna Kea, Hawaii. Sun-Wed. 41 hrs. $535. Contact: USC.

August 26-28—**Primary Care Medicine: A Practical Approach.** Scripps Clinic and Research Foundation at Le Meridien Hotel Coronado Island, San Diego. Fri-Sun. 18 hrs. $225. Contact: Bonny A. Mower, Dept of Academic Affairs, 400S, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 457-8556.

September 8-10—**New Advances in Common Neurologic Disorders.** UCSD Division of Neurology at Catamaran Resort Hotel, San Diego. Thurs-Sat. 14 hrs. $300. Contact: Shirley Kolkey, Conference Coordinator, 3770 Tansy, San Diego 92121. (619) 453-6222.

September 15-18—**Decentralized Care of People With AIDS: An Educational Seminar for Developmental Approach.** Sonoma County Academic Foundation for Excellence at Flamingo Hotel, Santa Rosa. Thurs-Sun. $275. Contact: Mary Ellen Buechter, SCAFE, 3325 Chanate Rd, Santa Rosa, 95404. (707) 527-4121.

September 24—**Lumbar Spine Disease: A Practical Approach for the Primary Care Practitioner.** Scripps Clinic and Research Foundation at Amphitheater, La Jolla. Sat. 5 hrs. $50. Contact: Bonny A. Mower, Dept of Academic Affairs, Scripps Clinic and Research Foundation, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 457-8556.

(Continued on Page 651)

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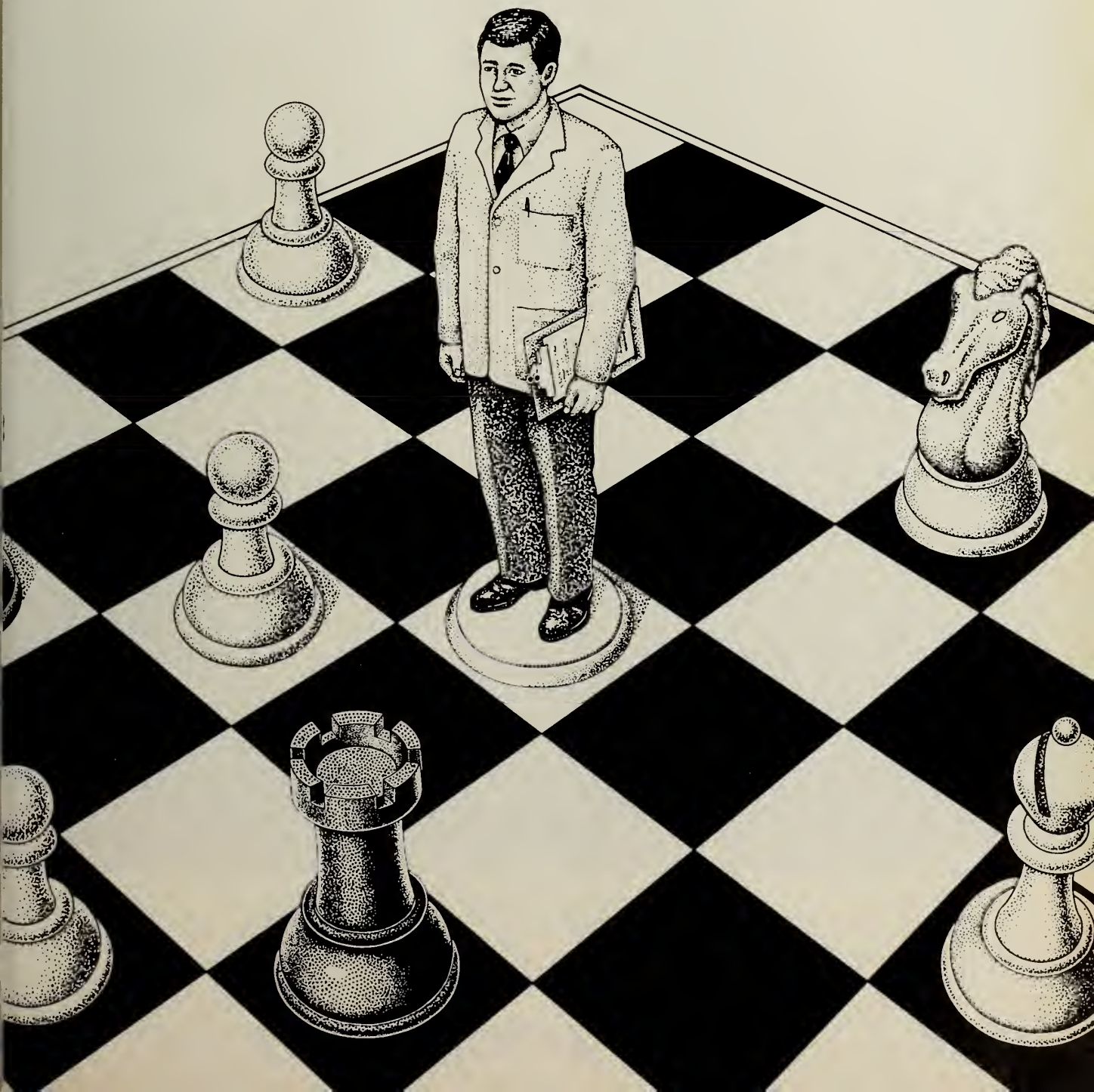

Glaxo

IN HYPERTENSION

resistance in the elderly[1]

- ☐ Effective blood pressure control
- ☐ Low incidence of fatigue,[2,3] impotence[2,3] and cold extremities[2-4]

Contraindicated in bronchial asthma, overt cardiac failure, greater-than-first-degree heart block, cardiogenic shock, and severe bradycardia.

See next page for references and Brief Summary of Product Information, which includes a listing of reported adverse reactions.

TRANDATE® *b.i.d.*

labetalol HCl/Glaxo *100 mg/200 mg tablets*

Because it also vasodilates

References: **1.** Holtzman JL, Finley D, Johnson B, et al: The effects of single-dose atenolol, labetalol, and propranolol on cardiac and vascular function. *Clin Pharmacol Ther* 1986;40:268-273. **2.** Due DL, Giguere GC, Plachetka JR: Postmarketing comparison of labetalol and propranolol in hypertensive patients. *Clin Ther* 1986;8(6):624-631. **3.** Burris JF, Goldstein J, Zager PG, et al: Comparative tolerability of labetalol versus propranolol, atenolol, pindolol, metoprolol, and nadolol. *J Clin Hypertens* 1986;3:1-9. **4.** Erb RJ, Plachetka JR: Thermographic evaluation of the peripheral vascular effects of labetalol and propranolol. *Curr Ther Res* 1985;28(1):68-73.

TRANDATE® Tablets
(labetalol hydrochloride)

BRIEF SUMMARY OF PRODUCT INFORMATION

The following is a brief summary only. Before prescribing, see complete prescribing information in TRANDATE® Tablets product labeling.

INDICATIONS AND USAGE: TRANDATE® Tablets are indicated in the management of hypertension. TRANDATE Tablets may be used alone or in combination with other antihypertensive agents, especially thiazide and loop diuretics.

CONTRAINDICATIONS: TRANDATE® Tablets are contraindicated in bronchial asthma, overt cardiac failure, greater-than-first-degree heart block, cardiogenic shock, and severe bradycardia (see **WARNINGS**).

WARNINGS: Cardiac Failure: Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure. Beta-blockade carries a potential hazard of further depressing myocardial contractility and precipitating more severe failure. Although beta-blockers should be avoided in overt congestive heart failure, if necessary labetalol HCl can be used with caution in patients with a history of heart failure who are well compensated. Congestive heart failure has been observed in patients receiving labetalol HCl. Labetalol HCl does not abolish the inotropic action of digitalis on heart muscle.

In Patients Without a History of Cardiac Failure: In patients with latent cardiac insufficiency, continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or be given a diuretic, and the response should be observed closely. If cardiac failure continues despite adequate digitalization and diuretic, TRANDATE® therapy should be withdrawn (gradually, if possible).

Exacerbation of Ischemic Heart Disease Following Abrupt Withdrawal: Angina pectoris has not been reported upon labetalol HCl discontinuation. However, hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy; exacerbation of angina and, in some cases, myocardial infarction have occurred after *abrupt* discontinuation of such therapy. When discontinuing chronically administered TRANDATE, particularly in patients with ischemic heart disease, the dosage should be gradually reduced over a period of one to two weeks and the patient should be carefully monitored. If angina markedly worsens or acute coronary insufficiency develops, TRANDATE administration should be reinstituted promptly, at least temporarily, and other measures appropriate for the management of unstable angina should be taken. Patients should be warned against interruption or discontinuation of therapy without the physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue TRANDATE therapy abruptly even in patients treated only for hypertension.

Nonallergic Bronchospasm (eg, Chronic Bronchitis and Emphysema): Patients with bronchospastic disease should, in general, not receive beta-blockers. TRANDATE may be used with caution, however, in patients who do not respond to, or cannot tolerate, other antihypertensive agents. It is prudent, if TRANDATE is used, to use the smallest effective dose, so that inhibition of endogenous or exogenous beta-agonists is minimized.

Pheochromocytoma: Labetalol HCl has been shown to be effective in lowering blood pressure and relieving symptoms in patients with pheochromocytoma. However, paradoxical hypertensive responses have been reported in a few patients with this tumor; therefore, use caution when administering labetalol HCl to patients with pheochromocytoma.

Diabetes Mellitus and Hypoglycemia: Beta-adrenergic blockade may prevent the appearance of premonitory signs and symptoms (eg, tachycardia) of acute hypoglycemia. This is especially important with labile diabetics. Beta-blockade also reduces the release of insulin in response to hyperglycemia; it may therefore be necessary to adjust the dose of antidiabetic drugs.

Major Surgery: The necessity or desirability of withdrawing beta-blocking therapy prior to major surgery is controversial. Protracted severe hypotension and difficulty in restarting or maintaining a heartbeat have been reported with beta-blockers. The effect of labetalol HCl's alpha-adrenergic activity has not been evaluated in this setting.

A synergism between labetalol HCl and halothane anesthesia has been shown (see **Drug Interactions** under **PRECAUTIONS**).

PRECAUTIONS: General: ***Impaired Hepatic Function:*** TRANDATE® Tablets should be used with caution in patients with impaired hepatic function since metabolism of the drug may be diminished.

Jaundice or Hepatic Dysfunction: On rare occasions, labetalol HCl has been associated with jaundice (both hepatic and cholestatic). It is therefore recommended that treatment with labetalol HCl be stopped immediately should a patient develop jaundice or laboratory evidence of liver injury. Both have been shown to be reversible on stopping therapy.

Information for Patients: As with all drugs with beta-blocking activity, certain advice to patients being treated with labetalol HCl is warranted. This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects. While no incidence of the abrupt withdrawal phenomenon (exacerbation of angina pectoris) has been reported with labetalol HCl, dosing with TRANDATE Tablets should not be interrupted or discontinued without a physician's advice. Patients being treated with TRANDATE Tablets should consult a physician at any sign of impending cardiac failure. Also, transient scalp tingling may occur, usually when treatment with TRANDATE Tablets is initiated (see **ADVERSE REACTIONS**).

Laboratory Tests: As with any new drug given over prolonged periods, laboratory parameters should be observed over regular intervals. In patients with concomitant illnesses, such as impaired renal function, appropriate tests should be done to monitor these conditions.

Drug Interactions: In one survey, 2.3% of patients taking labetalol HCl in combination with tricyclic antidepressants experienced tremor as compared to 0.7% reported to occur with labetalol HCl alone. The contribution of each of the treatments to this adverse reaction is unknown, but the possibility of a drug interaction cannot be excluded.

Drugs possessing beta-blocking properties can blunt the bronchodilator effect of beta-receptor agonist drugs in patients with bronchospasm; therefore, doses greater than the normal antiasthmatic dose of beta-agonist bronchodilator drugs may be required.

Cimetidine has been shown to increase the bioavailability of labetalol HCl. Since this could be explained either by enhanced absorption or by an alteration of hepatic metabolism of labetalol HCl, special care should be used in establishing the dose required for blood pressure control in such patients.

Synergism has been shown between halothane anesthesia and intravenously administered labetalol HCl. During controlled hypotensive anesthesia using labetalol HCl in association with halothane, high concentrations (3% or above) of halothane should not be used because the degree of hypotension will be increased and because of the possibility of a large reduction in cardiac output and an increase in central venous pressure. The anesthesiologist should be informed when a patient is receiving labetalol HCl.

Labetalol HCl blunts the reflex tachycardia produced by nitroglycerin without preventing its hypotensive effect. If labetalol HCl is used with nitroglycerin in patients with angina pectoris, additional antihypertensive effects may occur.

Drug/Laboratory Test Interactions: The presence of a metabolite of labetalol in the urine may result in falsely increased levels of urinary catecholamines when measured by a nonspecific trihydroxyindole (THI) reaction. In screening patients suspected of having a pheochromocytoma and being treated with labetalol HCl, specific radioenzymatic or high performance liquid chromatography assay techniques should be used to determine levels of catecholamines or their metabolites.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term oral dosing studies with labetalol HCl for 18 months in mice and for two years in rats showed no evidence of carcinogenesis. Studies with labetalol HCl using dominant lethal assays in rats and mice and exposing microorganisms according to modified Ames tests showed no evidence of mutagenesis.

Pregnancy: ***Teratogenic Effects: Pregnancy Category C:*** Teratogenic studies have been performed with

TRANDATE® Tablets (labetalol hydrochloride)

labetalol in rats and rabbits at oral doses up to approximately six and four times the maximum recommended human dose (MRHD), respectively. No reproducible evidence of fetal malformations was observed. Increased fetal resorptions were seen in both species at doses approximating the MRHD. There are no adequate and well-controlled studies in pregnant women. Labetalol should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects: Infants of mothers who were treated with labetalol HCl during pregnancy did not appear to be adversely affected by the drug. Oral administration of labetalol to rats during late gestation through weaning at doses of two to four times the MRHD caused a decrease in neonatal survival.

Labor and Delivery: Labetalol HCl given to pregnant women with hypertension did not appear to affect the usual course of labor and delivery.

Nursing Mothers: Small amounts of labetalol (approximately 0.004% of the maternal dose) are excreted in human milk. Caution should be exercised when TRANDATE Tablets are administered to a nursing woman.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: Most adverse effects are mild, transient, and occur early in the course of treatment. In controlled clinical trials of three to four months' duration, discontinuation of TRANDATE® Tablets due to one or more adverse effects was required in 7% of all patients. In these same trials, beta-blocker control agents led to discontinuation in 8% to 10% of patients, and a centrally acting alpha-agonist in 30% of patients.

The following adverse reactions were derived from multi-center, controlled clinical trials over treatment periods of three and four months. The rates, which ranged from less than 1% to 5% except as otherwise noted, are based on adverse reactions considered probably drug-related by the investigator. If all reports are considered, the rates are somewhat higher (eg, dizziness, 20%; nausea, 14%; fatigue, 11%).

Body as a Whole: Fatigue, asthenia, and headache.

Gastrointestinal: Nausea (6%), vomiting, dyspepsia, diarrhea, and taste distortion.

Central and Peripheral Nervous Systems: Dizziness (11%), paresthesia, and drowsiness.

Autonomic Nervous System: Nasal stuffiness, ejaculation failure, impotence, and increased sweating.

Cardiovascular: Edema and postural hypotension.

Respiratory: Dyspnea.

Skin: Rash.

Special Senses: Vision abnormality and vertigo.

The adverse effects were reported spontaneously and are representative of the incidence of adverse effects that may be observed in a properly selected hypertensive patient population, ie, a group excluding patients with bronchospastic disease, overt congestive heart failure, or other contraindications to beta-blocker therapy.

Clinical trials also included studies utilizing daily doses up to 2,400 mg in more severely hypertensive patients. The US therapeutic trials data base for adverse reactions that are clearly or possibly dose-related shows that the following side effects increased with increasing dose: dizziness, fatigue, nausea, vomiting, dyspepsia, paresthesia, nasal stuffiness, ejaculation failure, impotence, and edema.

In addition, a number of other less common adverse events have been reported in clinical trials or the literature:

Cardiovascular: Postural hypotension, including rarely, syncope.

Central and Peripheral Nervous Systems: Paresthesias, most frequently described as scalp tingling. In most cases, it was mild, transient, and usually occurred at the beginning of treatment.

Collagen Disorders: Systemic lupus erythematosus; positive antinuclear factor (ANF).

Eyes: Dry eyes.

Immunological System: Antimitochondrial antibodies.

Liver and Biliary System: Cholestasis with or without jaundice.

Musculoskeletal System: Muscle cramps; toxic myopathy.

Respiratory System: Bronchospasm.

Skin and Appendages: Rashes of various types, such as generalized maculopapular, lichenoid, urticarial, bullous lichen planus, psoriaform, and facial erythema; Peyronie's disease; reversible alopecia.

Urinary System: Difficulty in micturition, including acute urinary bladder retention.

Following approval for marketing in the United Kingdom, a monitored release survey involving approximately 6,800 patients was conducted for further safety and efficacy evaluation of this product. Results of this survey indicate that the type, severity, and incidence of adverse effects were comparable to those cited above.

Potential Adverse Effects: In addition, other adverse effects not listed above have been reported with other beta-adrenergic blocking agents.

Central Nervous System: Reversible mental depression progressing to catatonia, an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance or neuropsychometrics.

Cardiovascular: Intensification of AV block (see **CONTRAINDICATIONS**).

Allergic: Fever combined with aching and sore throat; laryngospasm; respiratory distress.

Hematologic: Agranulocytosis; thrombocytopenic or nonthrombocytopenic purpura.

Gastrointestinal: Mesenteric artery thrombosis; ischemic colitis.

The oculomucocutaneous syndrome associated with the beta-blocker practolol has not been reported with labetalol HCl.

Clinical Laboratory Tests: There have been reversible increases of serum transaminases in 4% of patients treated with labetalol HCl and tested, and more rarely, reversible increases in blood urea.

OVERDOSAGE: Information concerning possible overdosage and its treatment appears in the full prescribing information.

DOSAGE AND ADMINISTRATION: DOSAGE MUST BE INDIVIDUALIZED. The recommended *initial* dosage is 100 mg *twice* daily whether used alone or added to a diuretic regimen. After two or three days, using standing blood pressure as an indicator, dosage may be titrated in increments of 100 mg bid every two or three days. The usual *maintenance* dosage of labetalol HCl is between 200 and 400 mg *twice* daily. Before use, see complete prescribing information for dosage details.

HOW SUPPLIED: TRANDATE® Tablets, 100 mg, light orange, round, scored, film-coated tablets engraved on one side with "TRANDATE 100 GLAXO," bottles of 100 (NDC 0173-0346-43) and 500 (NDC 0173-0346-44) and unit dose packs of 100 tablets (NDC 0173-0346-47).

TRANDATE Tablets, 200 mg, white, round, scored, film-coated tablets engraved on one side with "TRANDATE 200 GLAXO," bottles of 100 (NDC 0173-0347-43) and 500 (NDC 0173-0347-44) and unit dose packs of 100 tablets (NDC 0173-0347-47).

TRANDATE Tablets, 300 mg, peach, round, scored, film-coated tablets engraved on one side with "TRANDATE 300 GLAXO," bottles of 100 (NDC 0173-0348-43) and 500 (NDC 0173-0348-44) and unit dose packs of 100 tablets (NDC 0173-0348-47).

TRANDATE Tablets should be stored between 2° and 30°C (36° and 86°F). TRANDATE Tablets in the unit dose boxes should be protected from excessive moisture.

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September 1986

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CONTINUING MEDICAL EDUCATION

(Continued from Page 646)

September 28-30—**Primary Care Medicine: Principles and Practice.** UCSF at the Portman Hotel, San Francisco. Wed-Fri. $365. Contact: UCSF.

October 10-14—**Current Topics in Occupational Medicine.** UCSF at Cathedral Hill Hotel, San Francisco. Mon-Fri. 40 hrs. $550. Contact: UCSF.

October 15-18—**Infectious Diseases: Part I of II.** EPIC Expeditions at Napa Valley. Sun-Tues. 12 hrs. Contact: EPIC Expeditions, PO Box 209, Sun Valley, ID 83353. (208) 788-4995.

October 19-22—**Infectious Diseases: Part II.** EPIC Expeditions at Sonoma Valley. Wed-Sun. 12 hrs. Contact: EPIC Expeditions, PO Box 209, Sun Valley, ID 83353. (208) 788-4995.

October 20-22—**Recent Advances in Pulmonary and Critical Care Medicine.** UCSF at Mark Hopkins Hotel, San Francisco. Thurs-Sat. 15 hrs. $365. Contact: UCSF.

October 21-23—**Office Orthopaedics for the Primary Care Physician.** Sharp Memorial Hospital at San Diego Princess. Fri-Sun. 20 hrs. $395. Contact: Jacqueline Shiller, Medical Education, PO Box 84296, San Diego 92138. (619) 223-2997.

November 10-13—**Sexual Literacy: What is it? What do we know? What do we need to know? Whose responsibility is it?** The Society for the Scientific Study of Sex at the Cathedral Hill Hotel, San Francisco. Thurs-Sun. Contact: Bernard Goldstein, San Francisco State University, Biology Dept., 1600 Holloway Ave., San Francisco, 94132. (415) 338-1548.

November 11-14—**The Spine: Current Concepts of Diagnosis and Treatment.** Spine Study Group at Marriott Desert Springs Resort, Palm Springs. Fri-Mon. $250. Contact: Spine Study Group, PO Box 33185, San Diego 92103. (619) 692-9115.

November 16—**Common Musculoskeletal Problems.** Veterans Administration Medical Center, Sepulveda. Wed. 6 hrs. Contact: Arun J. Mehta, MD, Rehabilitation Medicine Service (117), VA Medical Center, Sepulveda 91343. (818) 891-2473.

IDAHO

July 21-23—**Idaho Medical Association Annual Meeting.** Sun Valley. Thurs-Sat. Contact: IMA, 305 W. Jefferson, PO Box 2668, Boise 83701. (208) 344-7888.

August 6-13—**Acute and Emergency Medicine.** University of Arizona College of Medicine, Department of Family and Community Medicine, and Epic Expeditions at Sun Valley. 24 hrs. Contact: Kathy Rairigh, EPIC Expeditions, PO Box 209, Sun Valley, ID 83353. (208) 788-4995.

August 29-30—**Northwest Regional Perinatal Conference—Current Issues in Ob/Gyn, Neonatology and Pediatrics.** Inland Empire Perinatal Center at Coeur d'Alene Resort. Contact: Inland Empire Perinatal Center, 411 Medical Center Bldg, Spokane, WA 99204. (509) 624-3182.

September 2-5—**Strategies for Fitness and Health Promotion.** University of Arizona College of Medicine, Department of Family and Community Medicine, and Epic Expeditions at Sun Valley. 12 hrs. Contact: Kathy Rairigh, EPIC Expeditions, PO Box 209, Sun Valley, ID 83353. (208) 788-4995.

MONTANA

September 29-October 1—**Montana Medical Association Annual Meeting.** Heritage Inn, Great Falls. Fri-Sat. Contact: MMA, 2012 11th Ave., Suite 12, Helena 59601. (406) 443-4000.

(Continued on Page 731)

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Contraindications: *Concomitant use with other potassium-sparing agents such as spironolactone or amiloride. Further use in anuria, progressive renal or hepatic dysfunction, hyperkalemia. Pre-existing elevated serum potassium. Hypersensitivity to either component or other sulfonamide-derived drugs.*
Warnings: ***Do not use potassium supplements, dietary or otherwise, unless hypokalemia develops or dietary intake of potassium is markedly impaired.*** *If supplementary potassium is needed, potassium tablets should not be used. Hyperkalemia can occur, and has been associated with cardiac irregularities. It is more likely in the severely ill, with urine volume less than one liter/day, the elderly and diabetics with suspected or confirmed renal insufficiency. Periodically, serum K^+ levels should be determined. If hyperkalemia develops, substitute a thiazide alone, restrict K^+ intake.* ***Associated widened QRS complex or arrhythmia requires prompt additional therapy.*** *Thiazides cross the placental barrier and appear in cord blood. Use in pregnancy requires weighing anticipated benefits against possible hazards, including fetal or neonatal jaundice, thrombocytopenia, other adverse reactions seen in adults. Thiazides appear and triamterene may appear in breast milk. If their use is essential, the patient should stop nursing. Adequate information on use in children is not available. Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma. Possible exacerbation or activation of systemic lupus erythematosus has been reported with thiazide diuretics.*
Precautions: *The bioavailability of the hydrochlorothiazide component of 'Dyazide' is about 50% of the bioavailability of the single entity. Theoretically, a patient transferred from the single entities of triamterene and hydrochlorothiazide may show an increase in blood pressure or fluid retention. Similarly, it is also possible that the lesser hydrochlorothiazide bioavailability could lead to increased serum potassium levels. However, extensive clinical experience with 'Dyazide' suggests that these conditions have not been commonly observed in clinical practice. Angiotensin-converting enzyme (ACE) inhibitors can elevate serum potassium; use with caution with 'Dyazide'. Do periodic serum electrolyte determinations (particularly important in patients vomiting excessively or receiving parenteral fluids, and during concurrent use with amphotericin B or corticosteroids or corticotropin[ACTH]). Periodic BUN and serum creatinine determinations should be made, especially in the elderly, diabetics or those with suspected or confirmed renal insufficiency. Cumulative effects of the drug may develop in patients with impaired renal function. Thiazides should be used with caution in patients with impaired hepatic function. They can precipitate coma in patients with severe liver disease. Observe regularly for possible blood dyscrasias, liver damage, other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving triamterene, and leukopenia, thrombocytopenia, agranulocytosis, and aplastic and hemolytic anemia have been reported with thiazides. Thiazides may cause manifestation of latent diabetes mellitus. The effects of oral anticoagulants may be decreased when used concurrently with hydrochlorothiazide; dosage adjustments may be necessary. Clinically insignificant reductions in arterial responsiveness to norepinephrine have been reported. Thiazides have also been shown to increase the paralyzing effect of nondepolarizing muscle relaxants such as tubocurarine. Triamterene is a weak folic acid antagonist. Do periodic blood studies in cirrhotics with splenomegaly. Antihypertensive effects may be enhanced in post-sympathectomy patients. Use cautiously in surgical patients. Triamterene has been found in renal stones in association with the other usual calculus components. Therefore, 'Dyazide' should be used with caution in patients with histories of stone formation. A few occurrences of acute renal failure have been reported in patients on 'Dyazide' when treated with indomethacin. Therefore, caution is advised in administering nonsteroidal anti-inflammatory agents with 'Dyazide'. The following may occur: transient elevated BUN or creatinine or both, hyperglycemia and glycosuria (diabetic insulin requirements may be altered), hyperuricemia and gout, digitalis intoxication (in hypokalemia), decreasing alkali reserve with possible metabolic acidosis. 'Dyazide' interferes with fluorescent measurement of quinidine. Hypokalemia is uncommon with 'Dyazide', but should it develop, corrective measures should be taken such as potassium supplementation or increased dietary intake of potassium-rich foods. Corrective measures should be instituted cautiously and serum potassium levels determined. Discontinue corrective measures and 'Dyazide' should laboratory values reveal elevated serum potassium. Chloride deficit may occur as well as dilutional hyponatremia. Concurrent use with chlorpropamide may increase the risk of severe hyponatremia. Serum PBI levels may decrease without signs of thyroid disturbance. Calcium excretion is decreased by thiazides. 'Dyazide' should be withdrawn before conducting tests for parathyroid function. Thiazides may add to or potentiate the action of other antihypertensive drugs. Diuretics reduce renal clearance of lithium and increase the risk of lithium toxicity.*
Adverse Reactions: *Muscle cramps, weakness, dizziness, headache, dry mouth; anaphylaxis, rash, urticaria, photosensitivity, purpura, other dermatological conditions; nausea and vomiting, diarrhea, constipation, other gastrointestinal disturbances; postural hypotension (may be aggravated by alcohol, barbiturates, or narcotics). Necrotizing vasculitis, paresthesias, icterus, pancreatitis, xanthopsia and respiratory distress including pneumonitis and pulmonary edema, transient blurred vision, sialadenitis, and vertigo have occurred with thiazides alone. Triamterene has been found in renal stones in association with other usual calculus components. Rare incidents of acute interstitial nephritis have been reported. Impotence has been reported in a few patients on 'Dyazide', although a causal relationship has not been established.*
Supplied: ***'Dyazide' is supplied as a red and white capsule, in bottles of 1000 capsules; Single Unit Packages (unit-dose) of 100 (intended for institutional use only); in Patient-Pak™ unit-of-use bottles of 100.***

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Ibuprofen Overdose—A Prospective Study

ALAN H. HALL, MD; SUSAN C. SMOLINSKE, RPh; KENNETH W. KULIG, MD; *and* BARRY H. RUMACK, MD, *Denver*

Of 61 cases of ibuprofen overdosage reported consecutively to the Rocky Mountain Poison and Drug Center from September 1985 through April 1986, 16 were excluded because of incomplete follow-up or concurrent medication ingestion. A toxic reaction developed in 7 (16%) of the remaining 45 patients. Nausea, vomiting, abdominal cramps, mild central nervous system depression, coma, tachycardia, apnea, metabolic acidosis with or without respiratory alkalosis, hematemesis, and oliguric renal failure were noted. Two of six adults had a toxic reaction, and one died. Among pediatric patients, 5/39 (13%) had a toxic reaction. Of patients whose ibuprofen ingestion was less than 104 mg per kg, none became ill. All patients in whom the time of ingestion was known (six of seven) and who had a toxic reaction did so within four hours of ingestion. An ibuprofen overdose, although usually benign, can occasionally produce serious toxicity.

(Hall AH, Smolinske SC, Kulig KW, et al: Ibuprofen overdose—A prospective study. West J Med 1988 Jun; 148:653-656)

Although ibuprofen is often a benign drug in overdosage,[1] the development of serious toxic effects has been reported.[2-5] In a previous combined retrospective and prospective study from the Rocky Mountain Poison and Drug Center (RMPDC), a 19% incidence of ibuprofen toxicity occurred in a series of 126 patients.[5] The present prospective study was carried out to further characterize the toxicity of ibuprofen overdose.

Patients and Methods

We collected prospectively 61 cases of ibuprofen ingestion reported consecutively to the RMPDC over a period of eight months (from September 1985 through April 1986). Data recorded on standard American Association of Poison Control Centers contact forms included demographic information and specified whether the ingested preparation was prescription or nonprescription; the amount of ibuprofen ingested per body weight (milligrams per kilogram); the presence and type of toxicity reported; the time from ingestion to the onset of a toxic reaction; levels of ibuprofen in plasma; and outcome.

The description of signs and symptoms was elicited by experienced poison information specialists using a checklist. Information about the amount ingested was confirmed both with the caller and the health care providers when patients were evaluated in a health care facility. In cases of evaluation by telephone only, the history of the amount ingested was repeatedly checked by methods commonly used by poison centers—that is, having the caller read the container label to the poison information specialist, counting the number of pills remaining in the container, subtracting the number of pills known to have been used from the number dispensed, and having the caller conduct a careful search for any spilled medications. If the amount of medication missing was later determined to be different from that reported during the initial call, the latter amount was used in calculations. All callers were specifically instructed to call back to the poison center immediately if a patient who had been asymptomatic at the time the case was closed by the poison information specialist later had symptoms. No such calls were received.

In all, 12 asymptomatic patients with a total recorded follow-up of one hour or less after ingestion were excluded from analysis because the outcome could not be adequately assessed. Four patients with a history of ingesting other medications in addition to ibuprofen were also excluded.

The 45 cases remaining in the study were divided into adult (16 years and older) and pediatric (0.8 to 3 years) subsets for comparison. There were no patients in this series between 3 and 16 years of age.

Results

Toxic reactions occurred in 7/45 patients (16%) with a history of pure ibuprofen overdosage. Among the 45 patients, 3 had vomiting; 3 had mild central nervous system (CNS) depression; and there was 1 case each of nausea, abdominal cramps, tachycardia, coma, apnea, metabolic acidosis, mixed metabolic acidosis and respiratory alkalosis, hematemesis, and oliguric renal failure, with more than one clinical effect noted in three cases.

Of the 39 pediatric patients, 5 (13%) had toxic reactions. Three of these children had only gastrointestinal symptoms—abdominal cramps, vomiting, or nausea—after ingesting 104, 130, and 131 mg per kg, respectively. The fourth child had gastrointestinal symptoms and mild CNS depression after ingesting 708 mg per kg and had an ibuprofen plasma concentration of 533 μg per ml one hour after ingestion (therapeutic range from the laboratory doing the assay: 10 to 50 μg per ml). The fifth had vomiting, lethargy, transient periods of apnea, and metabolic acidosis (pH 7.27; partial carbon dioxide pressure [Pco_2] 36 torr) after in-

From the Clinical Toxicology Program (Drs Hall and Kulig) and the POISINDEX Information System (Ms Smolinske), Rocky Mountain Poison and Drug Center (Dr Rumack), and the Department of Pediatrics (Drs Hall and Rumack), University of Colorado Health Sciences Center, and the Denver General Hospital, Denver.

At the time of this investigation, Dr Hall was the recipient of a McNeil Fellowship in Clinical Toxicology.

Presented at the American Association of Poison Control Centers/American Academy of Clinical Toxicology/American Board of Medical Toxicology/Canadian Association of Poison Control Centers Annual Scientific Meeting, Santa Fe, September 1986.

Reprint requests to Barry H. Rumack, MD, Director, Rocky Mountain Poison and Drug Center, 645 Bannock St, Denver, CO 80204-4507.

ABBREVIATIONS USED IN TEXT

BUN = blood urea nitrogen
P_{CO_2} = partial carbon dioxide pressure
RMPDC = Rocky Mountain Poison and Drug Center
SEM = standard error of the mean

gesting 666 mg per kg. The ibuprofen plasma concentration was 680 μg per ml 3½ hours after ingestion. (This case has been previously reported by the treating physicians.[6])

There were no deaths or permanent sequelae in children. Symptomatic children had a mean (± standard error of the mean [SEM]) drug ingestion of 348 ± 139 mg per kg, whereas in asymptomatic children the mean ibuprofen ingestion was 135 ± 19 mg per kg.

Two of the six adult patients had toxic reactions. One of these had ingested an undetermined amount of ibuprofen and had transient mild CNS depression. The other, a 64-year-old man who had ingested forty 600-mg ibuprofen tablets (24 grams; 407 mg per kg) during the course of a day, was seen in the emergency department the same evening with confusion, tachycardia (120 beats per minute) without hypotension, and Hematest-positive emesis. According to the history, no other drugs or agents had been ingested. His initial serum electrolyte values were as follows: sodium 130, potassium 4.6, chloride 98, and total carbon dioxide 13 mEq per liter (anion gap, 19 mEq per liter). Arterial blood gas determinations in the emergency department showed a pH of 7.47, a P_{CO_2} of 18 torr, and a bicarbonate of 13 mEq per liter. Gastric lavage was followed by the administration of activated charcoal and magnesium sulfate as a cathartic, and the patient was admitted to the intensive care unit. His level of consciousness deteriorated over the following few hours, and the patient became comatose. Oliguria was noted over the next three hours, at which time serum electrolyte levels still showed an anion gap of 17 mEq per liter. The blood urea nitrogen (BUN) value was 103 mg per dl and serum creatinine was 2.8 mg per dl. The patient's condition continued to deteriorate despite supportive measures: Oliguria continued, sepsis developed, and he died on the second hospital day. The patient's family had requested that neither hemodialysis nor resuscitative measures be carried out. The results of a toxicology screen and a salicylate assay on admission were subsequently reported to be normal. An ibuprofen plasma concentration of a specimen obtained at an unknown time more than 12 hours after ingestion was 15.8 μg per ml.

Seven ibuprofen plasma concentrations were measured in four patients included in the analysis. The specimens for six of these plasma levels from three patients were obtained at known times between one and ten hours after ingestion, and the data are shown in Figure 1.

Of the seven patients who had toxic reactions, the six for whom the time of ingestion was known became ill within four hours of ingestion. None of the patients who had ingested less than 104 mg per kg of ibuprofen became ill.

Seven pediatric and three adult patients ingested prescription preparations; one of seven children and two of three adults had toxic reactions. Three adults and 32 children ingested nonprescription preparations; four of the children but none of the adults became ill.

Discussion

Ibuprofen, 2-(4-isobutylphenyl)-propionic acid, is an anti-inflammatory, analgesic, and antipyretic medication available in the United States in both prescription and nonprescription preparations. Serious toxic effects caused by overdosage, including oliguric renal failure, apnea, bradycardia, hypotension, metabolic acidosis, seizures, and coma, have been previously reported.[2-5]

Known pharmacokinetic properties of ibuprofen in therapeutic doses include an elimination half-life (τ½) of about two hours (1.92 to 2.43), volume of distribution 0.11 to 0.19 liters per kg, rapid absorption (80% in ½ to 2 hours), and 90% to 99% protein binding.[8-12] Plasma concentrations in adults given a single 400-mg dose orally peak at about 29 μg per ml after 1½ hours, decrease to about 3 μg per ml after 8 hours, and become undetectable 12 hours after ingestion.[1] A single oral dose is completely excreted (90% as metabolites) in the urine over a 24-hour period.[10]

In an earlier combined retrospective and prospective RMPDC study of 126 patients with a history of pure ibuprofen ingestion, there was no correlation in adults between the amounts of ibuprofen reported by the patients to have been ingested and the development of toxic effects.[5] In the present series, the small adult sample size precluded a meaningful comparison of symptomatic and asymptomatic adult patients. The earlier study found a significant difference between the mean (± SEM) amounts (mg per kg) of ibuprofen reportedly ingested by symptomatic (440 mg per kg ± 146)

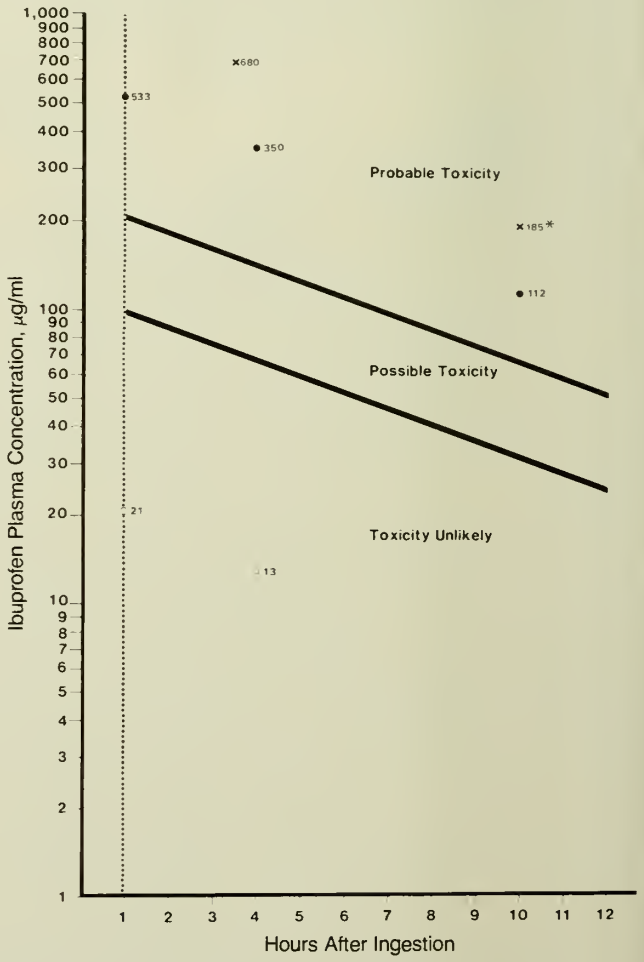

Figure 1.—Ibuprofen plasma concentrations in the present series are plotted on the ibuprofen nomogram developed from data in a previous study (from Hall et al[5]). *Ibuprofen plasma level taken from Lee and Finkler.[7] ○ = asymptomatic, • = mild symptoms, × = severe symptoms

and asymptomatic (114 mg per kg ± 19) children.[5] The mean amounts of the drug reported to have been ingested by children in the present series were 348 ± 139 mg per kg in symptomatic and 135 ± 19 mg per kg in asymptomatic patients, which are reasonably similar to those of the previous study.

There was one ibuprofen-related death among the children in the previous study.[5] There was no death among the children in the present series.

An ibuprofen nomogram (Figure 1) was developed from the earlier study data to aid in predicting which of the patients who are initially asymptomatic or mildly ill are at risk for the later development of more serious toxic reactions.[5] Plasma concentrations of ibuprofen in patients in the present series were compared with those in the nomogram to assess its predictive ability. The most seriously ill child had a plasma level of ibuprofen of 680 μg per ml 3½ hours after ingestion, which is in the "probable toxicity" area of the nomogram. A second child with gastrointestinal symptoms and mild CNS depression had plasma concentrations of the drug of 533 μg per ml after one hour, 350 μg per ml after four hours, and 112 μg per ml ten hours after ingestion, which are all in the "probable toxicity" range. An asymptomatic child had plasma concentrations of ibuprofen of 21 μg per ml after one hour and 13 μg per ml four hours after ingestion, which are both in the "toxicity unlikely" area. The nomogram thus accurately predicted the potential for the development of toxic reactions in the three patients from the present series in whom timed plasma concentrations of ibuprofen were determined.

One adult patient died after ingesting 24 grams of ibuprofen. There was no indication in the patient's history of concurrently ingesting other substances, and toxicology screening and salicylate assay results were normal. All previously reported cases of adults whose deaths were related to ibuprofen ingestion were complicated by concurrent ingestion of other substances, carbon monoxide poisoning, or exsanguination from self-inflicted wounds.[1] The specimen for determining the plasma ibuprofen concentration of 15.8 μg per ml was taken at an unknown time later than 12 hours after ingestion, and the level could only be used to verify the presence of the drug. It could not be compared with the levels on the nomogram.

In a recent case report, Lee and Finkler described a similar clinical course in a 48-year-old man who had ingested more than 20 grams of ibuprofen.[7] Coma, metabolic acidosis, mild hypotension, elevated BUN and creatinine levels, proteinuria and occult hematuria, mildly abnormal liver function, thrombocytopenia, and prolongation of both prothrombin and partial thromboplastin times were noted. No other agents were found on urine and blood toxicology screening. While the clinical course was complicated by acute renal failure, the adult respiratory distress syndrome, fever, and upper gastrointestinal tract bleeding, the patient survived with intensive supportive care.[7] The specimen for determining ibuprofen plasma level was obtained ten hours after ingestion, and the level was 185 μg per ml, which on the nomogram in Figure 1 falls in the "probable toxicity" area.

Adult patients ingesting between 6 and 54 grams of ibuprofen have been reported to have such symptoms and signs as nausea, vomiting, abdominal cramps, coma, elevated prothrombin and partial thromboplastin times, upper gastrointestinal tract bleeding, metabolic acidosis, and oliguric or nonoliguric renal insufficiency that required hemodialysis treatment in some cases.[2-4,7,13-15] It is currently unclear whether all adult patients who have taken an overdose of ibuprofen will become symptomatic within the first four hours after ingestion. Such patients have first come to medical attention between 1 and 48 hours after the ingestion, and the exact time of symptom onset was not reported in all cases.[2-5,7,13-15] The time of symptom onset following ingestion could not be determined in the patient in the present series who died.

Treatment of patients who have ingested an ibuprofen overdose is primarily supportive. Airway control and artificial ventilation, pulse and blood pressure support with fluids, the administration of atropine sulfate or vasopressors, correction of acidosis, and anticonvulsant therapy may be required. Gastric emptying may be beneficial soon after ingestion. Seizures have been reported in children in whom ibuprofen ingestion exceeded 400 mg per kg, and induced emesis may be dangerous in such cases.[5] Activated charcoal and a cathartic should be administered in an attempt to decrease drug absorption. Multiple-dose oral activated charcoal therapy has not yet been evaluated in ibuprofen overdosage.

Conclusion

Although many patients who ingest an overdose of ibuprofen remain asymptomatic, serious drug toxicity, including death from the complications of overdosage, occasionally occurs. Based on data from the medical literature, the previously published RMPDC study, and the present series, the following protocol is suggested as a rational way to proceed with assessment and referral of patients with an ibuprofen overdose.

Knowing the amount of drug ingested by adult patients is not predictive of the need for medical referral and observation. All symptomatic adults and those attempting suicide should be referred to a health care facility. Those who either remain actively suicidal or have any symptoms should be admitted to hospital until these conditions have cleared. Adult patients with no initial symptoms should be observed for a minimum of four hours in a controlled setting. If no symptoms develop during this period of observation, the decision to discharge patients not requiring admission for psychiatric reasons must be made on an individual basis. As the frequency of occurrence and time of onset of ibuprofen-induced renal insufficiency are presently poorly understood, obtaining baseline urinalysis, BUN, and serum creatinine values at the initial visit is suggested, with a follow-up evaluation scheduled for patients not admitted to hospital.

In children, the amount of ibuprofen ingested per body weight, as determined from the history, appears to be predictive of the potential for a toxic reaction developing and the need for medical referral. At levels of ingestion of less than 100 mg per kg, drug toxicity is unlikely to develop, and the children may be safely observed at home. Those ingesting 100 to 200 mg per kg may be managed with induced emesis and home observation for at least four hours, with referral to a health care facility reserved for those children in whom a toxic reaction develops. Children ingesting 200 to 400 mg per kg of ibuprofen should have immediate gastric emptying, activated charcoal and a cathartic administered, and they should be observed for at least four hours in a health care facility. Ingesting more than 400 mg per kg of the drug places

children at greater risk for a serious toxic reaction, and they should have immediate medical referral and careful observation, with supportive therapy as indicated by the clinical presentation and course. If gastric emptying is judged necessary, a gastric lavage is indicated instead of ipecac-induced emesis in children whose ibuprofen ingestion exceeds 400 mg per kg, because of the danger of convulsions and possible aspiration of gastric contents.

In both children and adults, the ibuprofen nomogram may be useful in predicting the potential for the development of drug toxicity and estimating its potential degree of severity when plasma levels can be measured.

The treatment of patients with ibuprofen overdosage is primarily supportive. Although uncommon, serious toxic reactions or death can result from an ibuprofen overdosage.

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Posttraumatic Syringomyelia

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Posttraumatic syringomyelia is becoming increasingly recognized as a sequel to major and minor spinal cord injury, paralleling the development and widespread availability of magnetic resonance imaging as a diagnostic modality for evaluating possible spinal pathologic lesions. Delayed, subacute, or progressive neurologic deterioration in victims of traumatic spinal injury with "fixed deficits" should raise the suspicion of posttraumatic syringomyelia. Alternatively, it may present as sensory or motor complaints occurring on a delayed basis after minor spinal trauma causing no initial neurologic impairment. At our institution, we have treated six of eight patients with this condition by shunting fluid from the intramedullary cyst to the peritoneal cavity by means of a simple valveless shunt, resulting in sustained neurologic improvement in five patients.

(LaHaye PA, Batzdorf U: Posttraumatic syringomyelia. West J Med 1988 Jun; 148:657-663)

Delayed formation of an intramedullary cavity as a sequel to spinal cord trauma has been recognized in the literature since the 19th century.[1] Protean in its clinical manifestations and presentation, posttraumatic syringomyelia may produce neurologic symptoms months to years after minor spinal trauma causing no initial neurologic impairment.[2] Alternatively, posttraumatic syringomyelia may represent the substrate for ascending[3] or anatomically remote[4] neurologic dysfunction in victims of traumatic paraplegia, occurring months to years after the onset of a "fixed neurologic deficit" consequent to the initial injury.

In a 1966 analysis of 591 patients with posttraumatic paraplegia,[5] a diagnosis of posttraumatic cavitation (syringomyelia) was made in 8 patients, representing an incidence of 1%. In 1981 alone, 24 new cases of posttraumatic syringomyelia were reported in the English language literature.[1,3,6] Three separate reports in 1983 and 1984 added a total of 61 cases to the literature.[7-9] Although no data are available to validly estimate the incidence of this condition, the longer survival of patients with severe spinal injury[3] coupled with new diagnostic modalities for evaluating possible spinal cord lesions can account for the greatly increased recognition of posttraumatic syringomyelia in recent years. The improved diagnostic capabilities of computed tomography (CT) and magnetic resonance imaging (MRI) of the spinal canal and its contents have greatly facilitated the follow-up of patients with spinal cord injury and the diagnosis of syringomyelia. In this report we call attention to the importance of considering this diagnosis in patients with a history of spinal injury and to some of the clinical features of this condition. We will discuss current concepts of the diagnosis and management of this disorder.

There are several situations in which spinal cord cavitation or syringomyelia may develop; excellent comprehensive reviews of this subject are available.[10] We have chosen to limit the present discussion to the posttraumatic situation, realizing that many of the concepts can be extrapolated to the larger problem of syringomyelia in general.

Patients and Methods

Eight cases of posttraumatic spinal cord cavitation have been drawn from a larger group of patients that included syringomyelia due to other causes. Six of the cases were managed with cyst-to-peritoneal shunting. An additional two patients with posttraumatic syringomyelia have been managed nonoperatively (to this point in time).

Diagnostic Measures

Patients were studied with a variety of techniques, including conventional myelography using metrizamide, metrizamide-enhanced CT, endomyelography, and MRI in the axial and sagittal planes. The evaluation was tailored for each patient, and no one patient was studied with all of these diagnostic modalities.

Operative Technique

All patients underwent the same surgical procedure. A two-level laminectomy was done with the patient in a full left lateral position (Figure 1). The laminectomy was centered at the most caudal point of the cystic cavity as shown radiographically but cephalad to the attenuated brushlike termination of the cyst, when such was present. A midline dural opening was made. A midline myelotomy of the distended cord was carried out over a distance of about 3 mm. A catheter was inserted in a cephalad direction for a distance of about 2 cm. The dura was reapproximated and the catheter secured (Figure 2). The peritoneal cavity was entered through a standard muscle-splitting incision in the right upper quadrant to allow placement of a peritoneal catheter. A subcutaneous tunnel was then fashioned between the two incisions, and the catheter within the cyst was attached to the peritoneal catheter. Flow-restricting valves were not used. Wound closures were standard. All patients had an uneventful postoperative course.

Follow-up

The follow-up time has ranged from 12 to 60 months in all

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ABBREVIATIONS USED IN TEXT
CT = computed tomography
MRI = magnetic resonance imaging

patients. In some instances, postoperative radiographic or MRI studies have aided in this longitudinal assessment.

Results

An accurate clinical assessment of the results of treating posttraumatic syringomyelia is as difficult as in patients with other forms of syringomyelia. The length of time between cord injury and treatment, the duration of symptoms attributable to the cavity rather than to the original injury, and the severity and type of neurologic deficit at the time of the operation all have a bearing on the overall outcome.

All patients showed evidence of neurologic improvement following the cyst-to-peritoneal shunting. One patient (case 3) showed dramatic albeit transient abatement of disabling autonomic dysreflexia that recurred later due to a visceral triggering mechanism. The other patients have shown sustained improvement in their neurologic condition as a result of the surgical procedure. Table 1 provides a summary of the clinical data regarding this group of patients. The following case reports illustrate the spectrum of clinical presentation, diagnostic evaluation, and outcome of treatment.

Reports of Cases

Case 1. In 1964, at age 23, this patient sustained a neck injury while diving into a pool. He experienced no motor or sensory deficit, but felt electric-shocklike sensations throughout his body for several hours. Radiographs were not taken, and he was treated with cervical traction. Persistent interscapular pain without neurologic deficit led to a T1-T2 posterior fusion in 1970. He began having neurologic problems in 1974 with clumsiness and atrophy of the right hand. A minor auto accident in 1979 was followed by the develop-

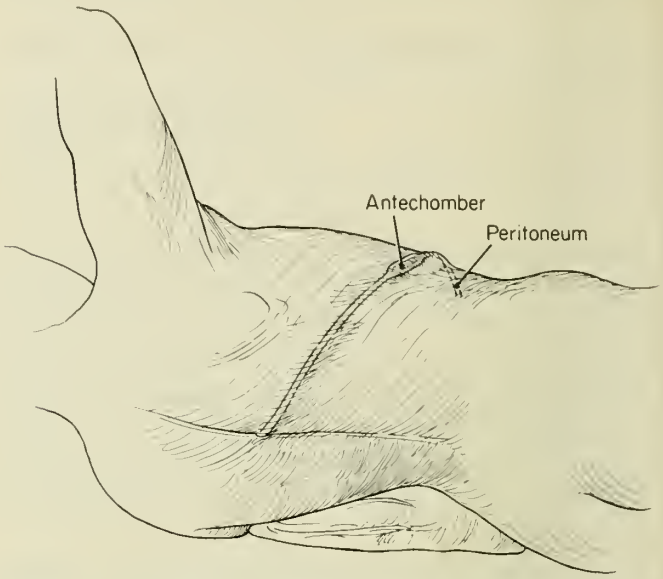

Figure 1.—The position of patient on an operating table shows the location of the antechamber over the lateral thoracic wall. This in-line antechamber allows access to the percutaneous system postoperatively.

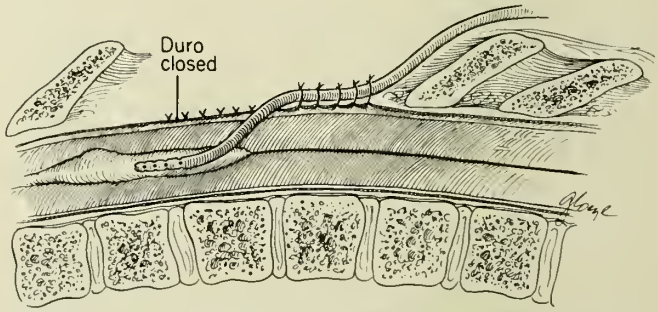

Figure 2.—The drawing shows the technique of securing shunt tubing to the dura for placing the cyst-to-peritoneal shunt.

TABLE 1.—*Clinical Summary of 8 Cases of Posttraumatic Syringomyelia*

Patient	Age, yr	Sex	Injury/Deficit	Interval to Onset of Symptoms	Neurologic Presentation	Diagnostic Studies (Year)	Treatment	Follow-up, yr	Outcome
1 . .	41	♂	Diving injury/none	10 yr	Hand atrophy; weakness; spasticity; neurogenic bladder	MTZ myelogram/CT, endomyelogram (1982)	Cyst-to-peritoneal shunt	5	Improved strength, gait; spasticity unchanged
2 . .	27	♂	Gunshot/L-1 paraplegia	12 yr	Hand weakness; sensory loss right face, arm, trunk	MTZ myelogram/CT (1982)	Cyst-to-peritoneal shunt	5	Improved strength; sensation unchanged
3 . .	39	♂	Diving injury/C-4 quadriplegia	10 yr	Autonomic dysreflexia; muscle spasms	MTZ myelogram/CT (1982)	Cyst-to-peritoneal shunt	5	Resolution of symptoms
4 . .	30	♂	Fall from moving vehicle/none	14 yr	Right leg pain; motor, sensory deficits; neurogenic bladder	MTZ myelogram/CT (1984)	Cyst-to-peritoneal shunt	3	All deficits lessened
5 . .	67	♀	Auto accident/none	3 mo	Lower extremity weakness;sensory loss; neurogenic bladder	MTZ myelogram/CT (1984)	Cyst-to-peritoneal shunt	3	Improved strength; decreased sensory deficit; neurogenic bladder
6 . .	55	♀	Fall from ladder/ transient left leg weakness	10 yr	Right arm weakness; Charcot joint, right shoulder	MRI (1985)	Operation declined	1	Unchanged
7 . .	17	♀	Auto accident/C-5 quadriplegia	6 mo	Progressive spasticity; episodic upper, lower extremity spasms	MRI (1985)	C-5 vertebrectomy and fusion	1	Increasing spasticity
8 . .	53	♀	Fall/none	2 yr	Right arm weakness and sensory deficit; mild spasticity	MRI (1986)	Cyst-to-peritoneal shunt	1	Improved strength and sensation; spasticity unchanged

CT=computed tomography, MRI=magnetic resonance imaging, MTZ=metrizamide

ment of paresthesias and weakness of the left hand. He had progressive gait deterioration with increased tone in the lower extremities beginning in 1980, along with troubling episodic spasms in the midthoracic region that gradually progressed caudally. Difficulty in initiating micturition developed, and the patient had several episodes of both urinary and fecal incontinence.

Two CT scans of the cervical and thoracic region were initially interpreted as inconclusive and as showing some degree of spondylosis in the cervical region. A third CT scan done in conjunction with a metrizamide myelogram revealed a cystic cavity within the cervical cord (Figure 3). A cyst puncture was then carried out with instillation of metrizamide, outlining the syrinx with its caudal tip at T-6 (Figure 4). A cyst-to-peritoneal shunting was done with subsequent improvement in left leg function and gait. The other neurologic deficits, including leg spasticity, have remained the same.

Case 2. In 1970, this patient sustained a gunshot wound of the spine at the T12-L1 level. He had immediate partial sensory and complete motor deficits at the L-1 level. He underwent a decompressive laminectomy and, with rehabilitation, became ambulatory with the aid of long-leg braces. He developed automatic bladder function. His neurologic condition remained stable until May 1982, when he noted numbness and a sensation of cold on the right side of the face, the right upper extremity, and the right side of the trunk. By June 1982, he noted difficulty with the use of his right hand for writing and other activities of daily living.

Myelography showed an enlarged cervical cord with widening present to the T-6 level consistent with an intramedullary cyst. A CT scan was confirmatory. The cord was not widened directly above the level of the original missile injury.

A cyst-to-peritoneal shunting was done in August 1982. His postoperative course was uneventful, and he has shown sustained improvement in the strength of his right upper extremity and is now able to write. Sensation has remained unchanged.

Case 3. In 1963, this 15-year-old boy sustained a C3-C4 fracture dislocation in a diving accident with resultant quadriplegia. His neurologic deficit was stable for the next decade.

In 1973, an autonomic dysreflexia began to develop, initially manifested as rigors and wide blood pressure fluctuations. His symptoms progressed over the next six years with the development of headache, facial flushing and hyperhidrosis, and truncal or lower extremity spasms triggered by simple tactile stimuli.

Metrizamide myelography and CT in 1982 revealed an extensive syrinx from C-4 to T-10. A cyst-to-peritoneal shunting afforded dramatic relief of symptoms.

In 1985 the patient had recurrent symptoms of autonomic dysreflexia. MR imaging, not available at the time of the first operation, showed that a septated portion of the syrinx had not been drained, and the shunt was modified accordingly. A subsequent recurrence of dysreflexia was attributed to cholelithiasis. Following cholecystectomy and splanchnicectomy as well as psychological support, his blood pressures stabilized, and he remains gainfully employed.

Case 4. This patient presented at age 30 with complaints of right lower extremity weakness and sensory loss. As an adolescent, he had fallen from a vehicle moving at 45 miles per hour, landing on the right side of his trunk with no resultant deficit. His symptoms began in 1980 with painful sensory loss in the right medial thigh aggravated with ac-

Figure 3.—Case 1: A 6-hour delayed computed tomographic scan shows accumulation of metrizamide within the cord.

Figure 4.—Case 1: An endomyelogram following the instillation of metrizamide shows narrowing at the caudal tip of the cyst.

tivity. Attendant weakness, atrophy, and sensory loss in that extremity led to myelography in 1982 that revealed total block at T-6. Surgical exploration showed "scar tissue," and his condition was unchanged after the procedure. Progressive motor and sensory deficits with new bladder, bowel, and sexual dysfunction led to his presentation to UCLA in 1984.

On neurologic examination he had both upper and lower motor neuron deficits in the right lower extremity and bilateral extensor plantar responses. A dissociated sensory loss below T-4 was demonstrable on the right side. Metrizamide myelography revealed a block at T-6 with widening of the cord caudally. On delayed CT scanning there was a syrinx from T-6 to T-10. Cyst-to-peritoneal shunting was done with improvement in micturition and lessened motor and sensory deficits in the right lower extremity.

Case 5. This 67-year-old woman was involved in a head-on auto accident in 1982. She suffered no immediate neurologic deficit but complained of neck and thoracolumbar pain from the date of injury. Within three months of the injury, paresthesias of both lower extremities developed, followed by right lower extremity weakness and bladder dysfunction. She remained ambulatory with the aid of a walker. The patient had a history of "trivial" episodes of trauma in another accident in 1974 and a fall in 1980.

On neurologic examination in 1984 she had weakness of both lower extremities, much more so on the right than the left. Plantar response was flexor bilaterally. A dissociated sensory loss was detected below the lower thoracic level. Metrizamide myelography and CT showed a syrinx with its caudal extent at T-11. A cyst-to-peritoneal shunting resulted in dramatic improvement in strength, lessened sensory impairment, and no change in bladder dysfunction.

Case 6. This 55-year-old woman presented with complaints of weakness and numbness of the right upper extremity and decreased range of motion at the right shoulder. Ten years before this evaluation, she had fallen from a ladder with transient left lower extremity weakness that resolved over weeks.

In 1982, the patient had a posterior dislocation of the right shoulder with relatively minor mechanical stress. In 1984, she began to note a "popping" sensation in the right shoulder and a painful numbness in the right upper extremity, with the subsequent development of atrophy and weakness in the right hand. She also noted numbness in the left lower extremity.

A neurologic examination revealed weakness and atrophy in the intrinsic musculature of the right hand. There was mild weakness in dorsiflexion and plantar flexion of the left foot. A dissociated sensory loss to pain and temperature was found on the right from C-6 to T-12 and below L-1 on the left. The right shoulder had a decreased passive range of motion.

Radiographs of the right shoulder revealed a Charcot joint, and MRI showed a cervicothoracic syrinx. Her major complaint on presentation to our service centered around the mechanical problems involving the right shoulder. Informed that such neuropathic changes would not be reversed by treatment of the syrinx and that her other deficits would remain stable or improve, she declined a shunting procedure. Her deficits have remained stable in 12 months of follow-up.

Case 7. This 17-year-old girl was involved in an auto accident in 1984, sustaining a burst fracture of C-5 with the immediate onset of quadriplegia. She was treated nonoperatively. Several months after injury, she had increasing spasticity and severe, painful spasms of the extensor musculature of the upper extremities and the flexor musculature of the lower extremities.

MRI seven months after injury revealed spinal cord compression at the C-5 level from a bony fragment of the fifth cervical vertebra. A low signal from the central region of the compressed cord was interpreted as myelomalacia or early cystic change.

In hopes of alleviating the disabling spasms, a C-5 vertebrectomy and fusion were done in 1985 but did not result in an improvement in neurologic signs or symptoms. On subsequent clinical follow-up she had a progressive increase in spasticity. Further MRI studies (Figure 5) have shown progressive cystic change within the spinal cord at this level. A surgical intervention has not been carried out to date. Her spasticity has been treated with a peripheral rhizotomy.

Case 8. This 53-year-old woman had a fall in 1980 with resultant neck pain but no neurologic deficit. Persistent cervical discomfort led to a brief series of chiropractic manipulations, halted because of exacerbation of pain. The pain resolved over the next several months without specific treatment. She had no further complaints until 1982, when she had painless "tingling" and numbness in the distal aspect of

Figure 5.—Case 7: Serial magnetic resonance imaging scans dated 7 months **(left)**, 14 months **(middle)**, and 21 months **(right)** after a cervical flexion injury. The anatomic evolution of this posttraumatic spinal cord cavity is clearly delineated.

the right upper extremity. This sensation slowly advanced proximally and by 1985 was accompanied by weakness and clumsiness in the same extremity.

On neurologic examination in 1986, she had right upper extremity weakness and mild bilateral lower extremity spasticity. A dissociated sensory loss was detected on the right from C-7 to T-8. MRI revealed a syrinx from the high cervical to the upper thoracic region. A cyst-to-peritoneal shunting was done, which decreased the motor and sensory deficits, but there was no change in spasticity. The neurologic improvement has been sustained in her relatively brief follow-up.

Discussion

Attempts have been made to correlate the development of posttraumatic syringomyelia with the severity of the initial spinal trauma. Posttraumatic syringomyelia has been reported in patients with complete[3] as well as partial cord lesions.[1,11] Of interest, only three of our eight patients showed a neurologic deficit at the time of injury. There does not appear to be a consistent relationship between the severity of the original injury and the subsequent development of an intramedullary cyst. A long interval—months to years—between spinal trauma and the appearance of neurologic symptoms is also characteristic of the condition and is amply documented in other case reports.[1,2,12]

In patients with a "fixed neurologic deficit" consequent to spinal cord injury, a posttraumatic syringomyelia manifests months to years later as exacerbation of existing motor and sensory deficits or ascending neurologic dysfunction. A long-term neurologic follow-up with detailed recording of the neurologic status will aid in the early detection of subtle deterioration and allow an early diagnostic evaluation and therapeutic intervention.

While neurologic deterioration that begins some months to years after injury of the spinal cord should raise concern about the possibility of posttraumatic syringomyelia, other pathologic processes can be responsible for the clinical changes observed. Instability of the spine at the site of injury, vascular thrombosis, arachnoid scarring, and the development of unrelated pathologic processes such as spondylosis, neoplasia, or a degenerative disorder of the nervous system must be included in the differential diagnosis.

In evaluating patients with new neurologic complaints indicative of spinal cord dysfunction and no preexisting deficit, it is important to seek a history of a blunt spinal trauma even months to years before the onset of symptoms. While relatively uncommon, posttraumatic syringomyelia must be included in the differential diagnosis, with a heightened level of suspicion in the presence of mixed upper and lower motor neuron deficits, dissociated sensory loss, and a neurogenic bladder. An insidious, progressive course seems characteristic of the condition.

Though a detailed discussion of the pathophysiology of posttraumatic syringomyelia is beyond the scope of this article and is reviewed elsewhere,[13] a few comments regarding the probable mechanisms of cyst formation are warranted. It has been suggested that cysts develop in areas of previous liquefaction necrosis or intraparenchymal hematomas.[3,12,14,15] While this is a likely operative mechanism of posttraumatic syringomyelia in some cases of severe spinal cord trauma, more subtle cord injuries—with some element of petechial hemorrhage or microinfarction—could set the stage for central myelomalacia and subsequent cavity formation. Enlargement of this cavity through the hydrostatic stresses of vigorous exercise, coughing, or sneezing can eventually lead to neurologic symptoms. Additionally, the tethering effect of local posttraumatic arachnoid scarring in limiting normal cord mobility and enhancing intramedullary stresses with the extremes of axial movement has been cited as a contributing factor in the extension and enlargement of these posttraumatic cavities.[13]

In most cases reported to date, the site of spinal trauma has been thoracic or upper lumbar, with the cyst extending cephalad from the level of injury. It is also apparent, however, that cysts may extend in either direction from the site of spinal injury, that they may be septated, and that separate cysts—one above and the other below the site of trauma—may occur. This latter condition may result from septa, adhesions, or canal stenosis at the level of injury.

While conventional myelography—by showing unusual

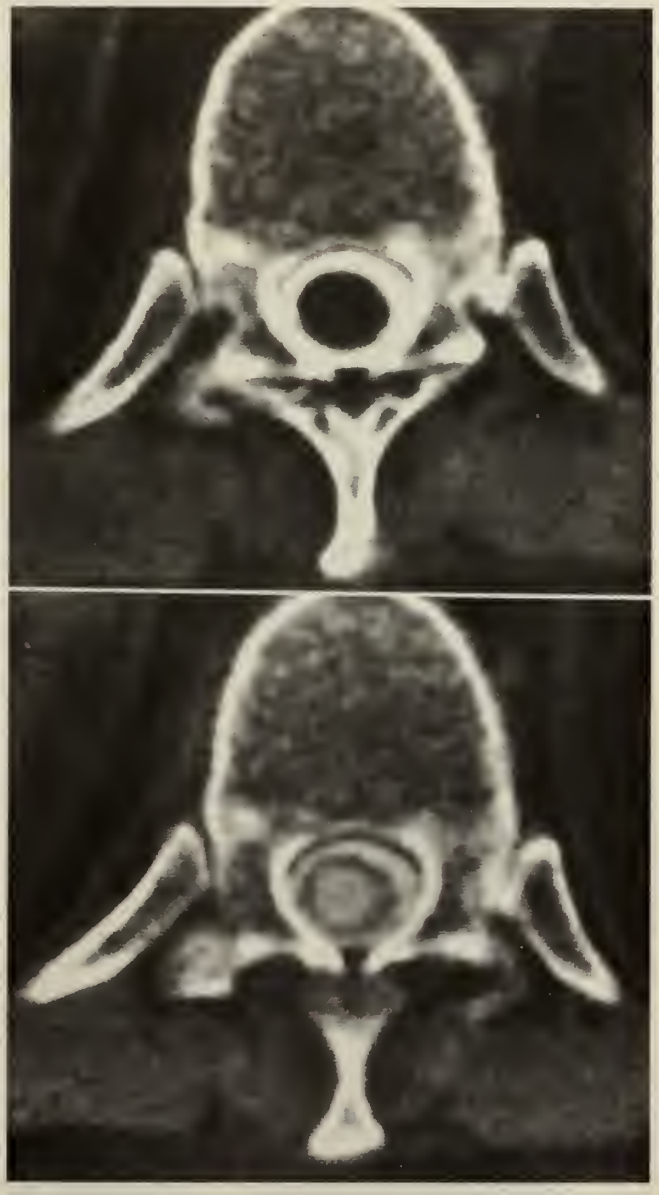

Figure 6.—Case 5: A computed tomographic (CT) scan after metrizamide myelography shows **(top)** an enlarged thoracic cord. A delayed CT scan **(bottom)** shows uptake of contrast within the intramedullary cyst.

widening of the spinal cord—may lead to the diagnosis, newer imaging techniques help to establish the precise cause of delayed neurologic deterioration. Metrizamide myelography in combination with CT scanning, including delayed views, offers an excellent means of demonstrating a cyst within the spinal cord (Figure 6). Delineating the lowest extent of the lesion is important to permit surgical drainage from the most caudal point of the cyst. When the precise anatomic outlines of the cyst are not satisfactorily delineated by CT scanning or MRI, direct cord puncture and instilling contrast material provide an excellent method of outlining the cyst.[16] The use of a water-soluble contrast medium offers a distinct improvement in so-called endomyelography.[17] The capability of sagittal and coronal imaging in addition to axial planes makes MRI especially appealing for studying posttraumatic syringomyelia (Figure 7). The noninvasive nature of magnetic resonance imaging also facilitates the longitudinal follow-up of patients with spinal cord injuries (Figure 5), as well as revealing collapse of the syrinx postoperatively (Figure 8).

It is apparent that with its present availability and sophistication, coupled with its noninvasive nature, MRI scanning is the diagnostic study of choice. Endomyelography is an invaluable adjunct for the evaluation of complex, septated lesions.

Because posttraumatic spinal cord cavities only rarely communicate with the fourth ventricle, the considerations that apply to their treatment differ from those that apply to congenital syringomyelia associated with a Chiari malformation. The aim of surgical treatment of posttraumatic syringomyelia is to establish drainage of the cyst, thus reducing the compression from within of surrounding functional spinal cord tissue. Drainage of the cyst thereby counteracts the forces that have been postulated to act in favor of cyst extension.

Over the years, several approaches have been used to achieve drainage of intramedullary cysts. These have included myelotomy,[7,14] cordectomy,[1,7,11,18] cyst-to-subarachnoid shunt,[1,7,19] and cyst-to-peritoneal shunt.[1,7,8,20,21] Currently, shunting procedures are the preferred method of surgical treatment. We have used cyst-to-peritoneal shunting exclusively as opposed to cyst-to-subarachnoid shunts. The dense arachnoidal adhesions associated with the posttraumatic situation can make shunting into the subarachnoid space difficult if not technically impossible in many cases. Further, cyst-to-peritoneal shunting without interposition of a flow-restricting valve enhances cyst drainage by capitalizing on pressure differentials between the intramedullary cavity and the free peritoneal cavity. With cyst-to-peritoneal shunting, percutaneous access to the system by means of an in-line antechamber allows the diagnosis of a suspected shunt malfunction or infection, distinct advantages over an inaccessible cyst-to-subarachnoid shunt.

Surgical drainage of a posttraumatic spinal cord cyst into the peritoneal cavity is an effective treatment modality, but it

Figure 7.—Case 8: A sagittal magnetic resonance image shows the intramedullary cavity.

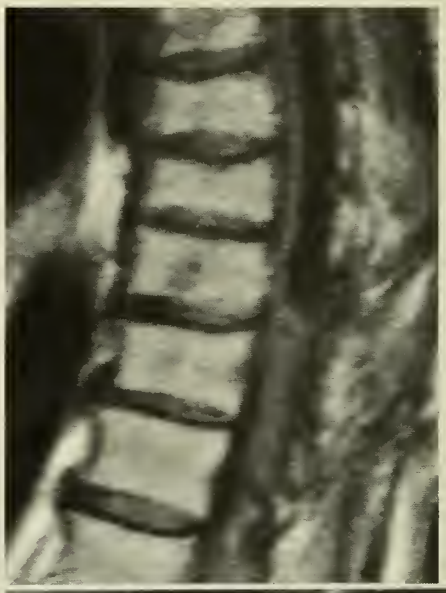

Figure 8.—Case 5: Magnetic resonance images taken postoperatively in the sagittal **(top)** and axial **(bottom)** planes show collapse of the syrinx.

should be reserved for those patients whose clinical syndrome is due to cord distention by cavity formation, with symptoms and signs appropriate to the demonstrated lesion. A progressive course certainly mandates therapy.

The burgeoning popularity and availability of MRI will certainly lead to the detection of a number of small, perhaps clinically silent, cases of posttraumatic syringomyelia. Treatment as herein described is only recommended if the lesion is clearly a source of neurologic morbidity.

Of the constellation of neurologic signs and symptoms attributable to posttraumatic syringomyelia, spasticity and dysesthetic pain (probably of central origin) seem least responsive to a shunting procedure. Aching local pain (probably due to distention of the cyst with resultant traction on pain-sensitive structures), motor deficits, and, to a lesser extent, sensory impairment are much more responsive to treatment. Progressive neurologic manifestations of this condition have been arrested, and in most instances patients' conditions are substantially improved as a result of this surgical procedure. This gratifying outcome has been sustained throughout follow-up periods.

Posttraumatic syringomyelia should be considered in any patient showing a delayed onset or progression of neurologic symptoms following spinal injury. The magnitude of the initial traumatic insult has no consonant bearing on the subsequent development of this disorder. Further, posttraumatic syringomyelia can be both temporally and spatially remote from spinal trauma. A clinical suggestion of posttraumatic syringomyelia and the thoughtful use of magnetic resonance imaging in evaluating these patients will lead to prompt diagnosis and appropriate referral. The cyst-to-peritoneal shunting offers effective treatment of this disorder.

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Clinical Review

Coronary Artery Vasospasm Complicating Acute Myocarditis

A Rare Association

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A 17-year-old boy had a 2-day prodrome of fever and mild sore throat followed by 2 episodes of severe anginal chest discomfort and substantial transient ST-segment elevations in the anterior leads of the electrocardiogram. A subsequent evaluation showed the 2 episodes were most likely coronary vasospasm complicating acute viral myocarditis.

(Ferguson DW, Farwell AP, Bradley WA, et al: Coronary artery vasospasm complicating acute myocarditis—A rare association. West J Med 1988 Jun; 148:664-669)

Acute viral myocarditis, while usually a relatively benign and self-limited disorder, has been associated with both short-term and long-term complications.[1] Diagnosing this disorder is often difficult, and there are many case reports of myocarditis masquerading as acute myocardial infarction.[2-11] The chest pain and electrocardiographic (ECG) changes characteristic of myocarditis have often been attributed to associated pericardial inflammation or direct inflammatory reaction in the myocardium. A common feature of these case reports has been the persistence of abnormal ECG patterns consistent with ischemia or infarction. We present the first well-documented case of coronary artery vasospasm with reversible transient ECG changes complicating the early stages of viral myocarditis. We review the variable presentations and reported complications of viral myocarditis, examine previous cases suggesting the association of vasospastic angina and myocarditis, and discuss the possible mechanisms of such a relationship.

Report of a Case

A previously healthy 17-year-old boy presented to a local hospital in July 1986 after being awakened from sleep at 3 AM with severe, crushing, substernal chest discomfort radiating to both arms and associated with diaphoresis and dyspnea. For the preceding two to three days he had had low-grade fever and mild sore throat without other symptoms. On admission to the local emergency department, an ECG showed 2 to 4 mm of upsloping ST-segment elevation in leads I, aV_L, and V_4 to V_6, and 1 to 2 mm of downsloping ST-segment depression in leads III and aV_F (Figure 1, upper panel). He was treated initially with a regimen of sublingual nitroglycerin, nifedipine, the topical application of nitroglycerin ointment, and intravenous morphine sulfate, resulting in resolution of the chest discomfort and near normalization of the electrocardiogram (Figure 1, lower panel). He was admitted to the coronary care unit at his local hospital, and therapy with diltiazem hydrochloride and oral indomethacin was begun for presumed myocarditis. The initial creatine kinase level was 454 IU per liter (normal 0 to 220) with a positive MB fraction.

The patient remained stable and free of any chest discomfort until 12 hours later when, while lying quietly in bed, he had the abrupt recurrence of severe chest discomfort radiating to both arms. A repeat electrocardiogram again showed 2 to 8 mm of upsloping ST-segment elevation in leads V_4 to V_6, I, II, and aV_L and 2 mm of downsloping ST-segment depression in leads V_1 and V_2 (Figure 2, upper panel). This second episode of chest discomfort was relieved within 20 minutes following the administration of sublingual nitroglycerin and nifedipine, topical nitroglycerin ointment, and intravenous morphine sulfate. A repeat electrocardiogram 30 minutes later after pain relief showed a significant reduction of the ST-segment abnormalities in the anterolateral leads (Figure 2, lower panel). The intravenous administration of nitroglycerin was begun, and the patient was transferred to the Medical Center Hospital of Vermont for further evaluation.

His medical history was entirely normal except for the usual childhood illnesses. He said he did not have a history of hypertension, diabetes mellitus, hyperlipidemia, or cardiovascular disease. There was no family history of cardiac disease, and he had had no symptoms of migraine headaches or Raynaud's phenomenon. The patient had smoked less than half a pack of cigarettes per day for several years, and he denied using cocaine or other drugs. He was taking no medication before being admitted to hospital.

On physical examination on arrival, he appeared anxious. His vital signs included a temperature of 37.5°C (99.5°F), pulse 120 beats per minute, and blood pressure 104/78 mm of mercury. The examination showed a few pea-sized,

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slightly tender, posterior cervical lymph nodes bilaterally without other peripheral adenopathy. The lungs were clear on auscultation, and a cardiac examination elicited prominent S_3 and S_4 gallops without murmurs, rubs, or clicks. There was no hepatosplenomegaly, and no other abnormalities of the abdomen were noted.

On admission, an ECG showed minimal (< 1 mm) ST-segment elevation in leads V_4 to V_6. A chest x-ray film was normal, and laboratory values included the following: hemoglobin 15.0 grams per dl, hematocrit 43.4%, leukocyte count 13,600 per μl (82% segmented neutrophils, 12% lymphocytes, and 6% monocytes), normal electrolytes and renal function, and a Westergren erythrocyte sedimentation rate of 32 mm per hour (normal 0 to 15). The initial creatine kinase level was 305 IU per liter (normal 2 to 82) with an MB fraction of 27 IU per liter, lactic dehydrogenase 247 units per liter (normal 60 to 200), and serum aspartate aminotransferase 84 units per liter (normal 0 to 41).

Hospital Course

Because of the uncertain clinical diagnosis and the suggestion of an intermittent acute coronary insufficiency syndrome, the patient was taken directly to the cardiac catheterization laboratory for diagnostic study. Right heart hemodynamics obtained with the patient receiving a continuous intravenous infusion of nitroglycerin at 48 μg per minute showed a right atrial pressure of 5 mm of mercury, a right ventricular pressure of 28/8 mm of mercury, a pulmonary artery pressure of 20/10 mm of mercury, a mean pulmonary artery pressure of 14 mm of mercury, and a pulmonary capillary wedge pressure of 11 mm of mercury. The central aortic pressure was 104/85 mm of mercury, heart rate 80 beats per minute, and thermodilution cardiac output 5.04 liters per minute. A left heart catheterization revealed a left ventricular end-diastolic pressure of 16 mm of mercury, and a biplane left ventricular cineangiography showed severe, diffuse, global hypokinesis with a calculated ejection fraction (area-length method) of 0.27. On coronary arteriography there was a normal left main trunk; a large, normal left anterior descending system; a small, normal left circumflex system; and a normal dominant right coronary artery (Figure 3).

The patient was admitted to the cardiac intensive care unit for observation and was maintained on a regimen of intravenous nitroglycerin and nifedipine given orally. His hemodynamic status remained stable and he had no significant arrhythmias. Serial ECGs revealed 1 to 2 mm of ST-segment elevation in the lateral precordial leads for 48 hours and then a return to normal, without any serial changes in the T waves or the development of pathologic Q waves. Cardiac enzyme values decreased serially from the initial levels on admission and by the third hospital day were normal. The morning after admission, a radionuclide ventriculogram showed moderately severe global hypokinesis of the left ventricle with an ejection fraction of 0.36 (normal > 0.55). An echocardiogram done the day after admission showed no evidence of pericardial effusion and no segmental wall motion abnormalities. A repeat radionuclide ventriculogram a week later showed normal ventricular function with a left ventricular

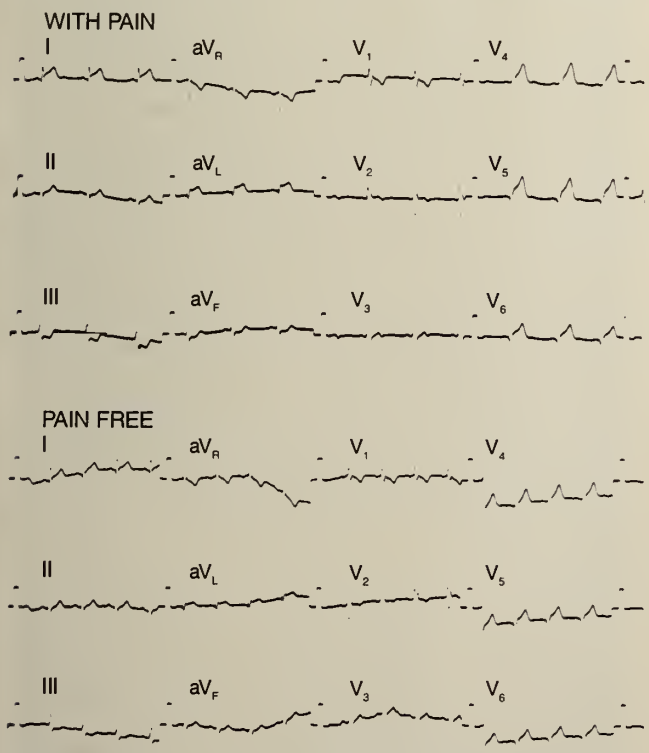

Figure 1.—The initial electrocardiograms taken on presentation to a local emergency department are shown. **Upper panel,** The tracing was obtained during the initial episode of chest pain and shows 2 to 4 mm of upsloping ST-segment elevation in leads I, aV_L, and V_4 to V_6 and 1 to 2 mm of downsloping ST-segment depression in leads III and aV_F. **Lower panel,** A repeat tracing taken 30 minutes later after therapy with complete resolution of chest discomfort shows near normalization of the electrocardiogram.

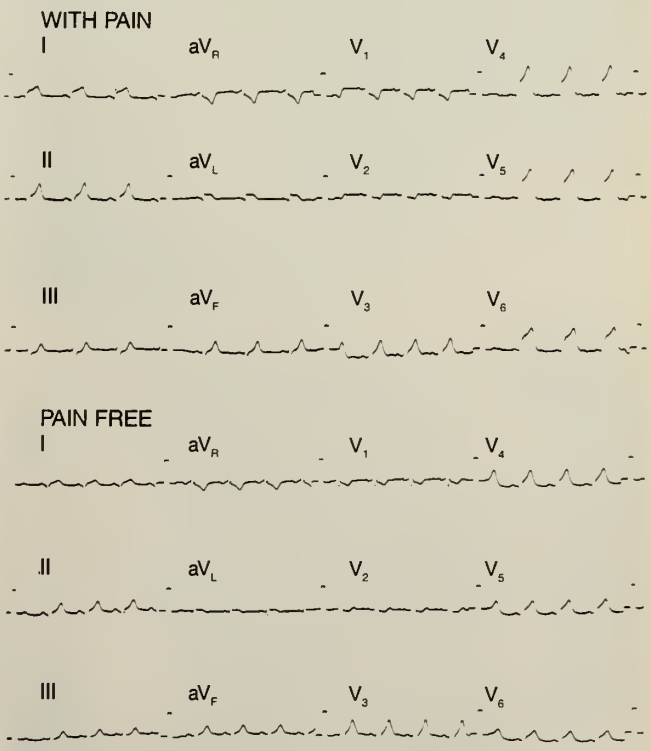

Figure 2.—Electrocardiograms were taken during and upon resolution of the second episode of acute chest pain and diaphoresis occurring at bed rest 12 hours after admission to the local hospital. **Upper panel,** Pronounced 2 to 8 mm of ST-segment elevation is shown in leads I, II, aV_L, and V_4 to V_6, and 2 mm of downsloping ST-segment depression occurs in leads V_1 and V_2 during chest pain. **Lower panel,** A repeat electrocardiogram shows significant resolution of the ST-segment changes 20 minutes after relief of the chest pain following therapy with nitroglycerin, nifedipine, and morphine sulfate.

ejection fraction of 0.59 and no focal or global wall motion abnormalities.

Diagnostic laboratory studies done during his hospital stay included several blood cultures, tests for hepatitis B antigen and antibody, a throat culture screen for *Streptococcus,* an antistreptolysin O titer, and a Monospot slide test on two occasions, all of which were negative. The rheumatoid factor was less than 10 IU per liter, and an antinuclear antibody titer was less than 20 dilutions. Urine viral cultures were negative, and acute and convalescent serum viral titers failed to definitively establish the causative viral agent.

The patient made an uneventful recovery without recurrent chest pain, fever, arrhythmias, or symptoms of heart failure. A 24-hour Holter monitor before hospital discharge revealed no arrhythmias and no ischemic ECG changes. Therapy with nifedipine, 10 mg given orally every eight hours, was continued, and the patient was discharged on the tenth day following admission. On follow-up evaluation as an outpatient at one month there was no recurrence of symptoms and no abnormalities on a physical examination. A subsequent follow-up over 12 months—initially while receiving nifedipine for 10 months and then after all medication had been discontinued for 2 months—revealed no recurrence of symptoms.

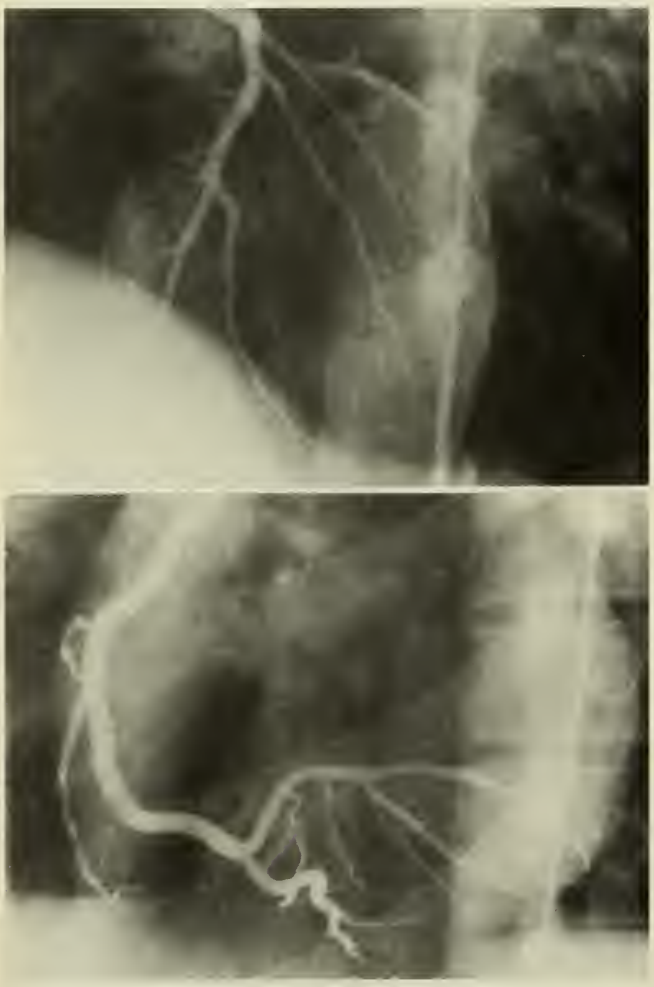

Figure 3.—Top, A selective left coronary arteriogram in the 40-degree left anterior oblique projection with cranial angulation shows normal left anterior descending and circumflex coronary arteries. **Bottom,** A selective right coronary arteriogram in the 40-degree left anterior oblique projection shows a normal dominant right coronary artery.

Discussion

In this report we present the case of a young male patient having clinical and electrocardiographic evidence of acute myocardial ischemia that was initially thought to be consistent with an acute anterior wall myocardial ischemic episode. Subsequent clinical, angiographic, electrocardiographic, and laboratory findings indicated the underlying process was most likely acute viral myocarditis. Of particular significance is the documentation of two separate brief episodes of severe ischemic chest pain associated with diaphoresis and dyspnea with recorded transient pronounced ST-segment elevations in the anterior leads of the ECG. These two episodes responded rapidly to the administration of nitrates and calcium channel blocking agents with a rapid relief of symptoms and a rapid resolution of the anterior lead ST-segment changes on the ECG. In association with the documented normal coronary arteries immediately after these episodes resolved, the clinical features appear most consistent with two episodes of coronary artery vasospasm—variant or Prinzmetal's angina—complicating the early stages of acute viral myocarditis. While there has been some conjecture in the literature regarding the possible association of vasospastic angina with acute myocarditis, this represents the first reported case, to our knowledge, of such well-documented transient but recurrent vasospastic ischemic events complicating the early stages of acute viral myocarditis.

Incidence, Presentation, and Complications of Myocarditis

The diagnosis of myocarditis has been a challenging and controversial problem since the term was first introduced by Sobernheim in 1837.[12(p117)] Postmortem studies have recorded active myocarditis in as high a frequency as 17% to 21% of young persons suffering sudden, unexpected, nonaccidental death.[13,14] The recent introduction and increasingly widespread use of percutaneous endomyocardial biopsy have allowed morphologic description and classification of myocarditis with some correlation of histologic findings and the clinical severity of the disease.[15-17] In most series, endomyocardial biopsy specimens have shown that anywhere from 6% to 29% of patients with idiopathic congestive cardiomyopathy have histologic evidence of lymphocytic myocarditis,[18-22] with some consecutive series suggesting an incidence as high as 63%.[23] In adolescents and young adults, the picornaviruses are the agents most frequently implicated in this disease.[1] Of these agents, the Coxsackie B viruses are associated with almost half of the cases wherein myopericarditis is established.[24-31] Most cases occur in the summer and fall months and much more commonly in men than in women.[1]

The clinical presentation of acute myocarditis is often one of fever, malaise, atypical chest pain, and exertional dyspnea. Regional ventricular wall motion is typically globally depressed with varying degrees of biventricular dilatation.[32] The clinical presentation, however, may mimic the symptoms of an acute myocardial infarction.[2-11] In addition, invasive and noninvasive assessments of regional left ventricular wall motion have occasionally shown focal abnormalities similar to those found in patients with acute myocardial infarction.[2,4-10]

While in most adult patients myocarditis is usually a mild disease,[1,33] numerous cardiac structural and electrical sequelae have been reported. These have included transmural

right and left ventricular myocardial necrosis,[3,4,34] transient segmental myocardial dyskinesis,[6] transient pseudohypertrophy of the ventricle due to edema,[35] isolated diastolic left ventricular dysfunction,[36] high-degree atrioventricular block,[4,37] hemiblocks and bundle branch blocks,[5] ventricular arrhythmias,[19,21,38] and sudden cardiac death.[39] Transient heart failure may complicate acute episodes of myocarditis, and, in addition, there is increasing evidence to suggest that a substantial number of cases of chronic dilated cardiomyopathy may be due to viral myocarditis.[1,40,41]

Previous Reports of Similar Cases

The patient in the case reported here presented with the clinical features of a threatened acute myocardial infarction. While the findings of normal coronary arteries at the time of an immediate catheterization argue against this causing his clinical presentation, they do not exclude it, for as many as 17% of confirmed myocardial infarctions in young patients occur in persons with angiographically normal coronary arteries.[42] The transient, nonfocal, global depression of left ventricular function, however, followed by a rapid recovery of systolic function within seven days and a return to normal of the ECG within 72 hours argues strongly against a classic myocardial infarction as the underlying process in this patient. The prodrome of fever and sore throat followed by acute severe global depression of myocardial function in a previously healthy young patient, combined with moderately elevated creatine kinase levels and the rapid recovery, is most consistent with acute viral myocarditis. The two discrete well-documented episodes of severe anginal chest pain, however, with transient notable ST-segment elevation in the anterior leads of the electrocardiogram are an unusual feature of this case and suggest a second pathophysiologic process—namely, vasospastic angina complicating the early stages of myocarditis.

Several previously reported cases have raised the question of coronary artery spasm complicating acute viral myocarditis, but none have reported recurrent transient episodes of severe chest pain with rapidly reversible ST-segment changes, as noted with the patient in this report. While this patient had a normal ECG on discharge, most cases described in the literature had prolonged electrocardiographic abnormalities. Take and co-workers evaluated the electrocardiographic changes in 16 cases of acute myocarditis confirmed by biopsy and found that 13 had ST-segment elevation initially and 10 went on to have Q waves.[43] The earliest return to normal of any patient's ECG was 15 days, while only five had a normal tracing on follow-up at 1 to 5 years. Chandraratna and associates described the case of a 19-year-old man presenting with two hours of anginalike chest pain following a two-day course of fever, sore throat, and arthralgias.[2] The initial ECG showed anterolateral ST-segment elevation, and sequential ECGs failed to show Q-wave development, but ST-segment and T-wave changes persisted. Cardiac enzyme values were elevated, consistent with myocardial necrosis. A cardiac catheterization done three months later showed normal coronary arteries before and after ergonovine maleate infusion and mild apical hypokinesis. Diamond and colleagues reported the case of a 23-year-old man presenting with severe retrosternal chest pain with an ECG suggestion of acute apical myocardial infarction following two days of fever and myalgias.[5] Influenza viral titers were subsequently shown to be suggestive of an acute viral myopericarditis. A cardiac catheterization done three weeks later showed normal coronary arteries and apical hypokinesis. The authors suggested an associated coronary arteritis or vasospasm might have been the underlying cause, but no supportive data were described. Costanzo-Nordin and co-workers described the case of a 17-year-old boy who for a week had sore throat, fever, palpitations, chest pressure discomfort that radiated to the left arm, and ECG findings of acute inferolateral myocardial infarction.[7] A cardiac catheterization done a week later revealed normal left ventricular wall motion and normal coronary arteries. The results of a right ventricular endomyocardial biopsy were compatible with active myocarditis.

Pasquini and associates reported the case of a 35-year-old man with fever, diaphoresis, and chest discomfort without a prodrome.[6] His initial ECG was normal, but recurrent chest pain the following day was accompanied by ST-segment elevation in the inferolateral leads, and a simultaneous echocardiogram revealed focal inferoapical dyskinesis. The chest pain responded partially to the administration of nitroglycerin and nifedipine. An immediate cardiac catheterization showed normal coronary arteries and inferoapical dyskinesis. Two days later, congestive heart failure and cardiogenic shock developed, but repeat angiography again showed normal coronary arteries with severe diffuse left ventricular hypokinesis. Management with intra-aortic balloon counterpulsation, inotropic agents, and the administration of azathioprine and corticosteroids was followed by complete recovery of left ventricular function, and a presumptive diagnosis of viral myocarditis was made. A suspicion was raised regarding focal viral-induced coronary arteritis causing the initial discrete inferoapical dyskinesis.

O'Neill and colleagues reported the cases of 12 patients with ECGs showing acute myocardial infarction and with serologic evidence of Coxsackie B infection.[11] Of these, 11 underwent catheterization and 7 were found to have normal coronary arteries. Three patients underwent ergonovine provocation testing and all were negative. The authors theorized that myocarditis was the cause of the myocardial damage in at least half of the patients. Finally, Miklozek and Abelman briefly described the cases of nine patients with viral myopericarditis who presented with acute myocardial infarction and who were subsequently found to have normal coronary arteries.[34] The possibility of an association between acute viral syndromes and myocardial infarction has been previously noted,[44,45] but this relationship has not been confirmed in other studies.[46,47]

In none of these previously reported cases were discrete episodes of ischemic chest pain and pronounced transient, reversible ST-segment elevations on the ECGs noted. This pattern, typical of coronary vasospasm, was a recurrent unique feature of the case presented herein.

Possible Mechanisms of Coronary Vasospasm During Myocarditis

Variant angina is classically defined as episodes of ischemic chest discomfort occurring at rest and associated with transient ST-segment elevations on the ECGs. Since initially described by Prinzmetal and co-workers, this disorder has been extensively studied.[48,49] Variant angina is thought to be due to coronary vasospasm superimposed on normal or atherosclerotic coronary arteries.[50-52] Episodic coronary vasospasm can occur with or without the conscious recognition of

chest pain and has been found to have some degree of circadian rhythmicity, with most episodes occurring in the early morning hours.[53] While usually described in adults, this disorder has been documented in patients as young as 11 years of age.[54] During spontaneously occurring episodes of variant angina, regional myocardial blood flow clearly decreases, coincident with the onset of angina and ST-segment changes.[55]

Several physical and pharmacologic factors have been associated with the occurrence of variant angina and coronary artery spasm. These include exercise,[56,57] cold exposure,[58] hyperventilation,[59] and alkalosis.[60] The known pharmacologic agents that provoke coronary vasospasm in patients include methacholine,[61,62] epinephrine,[61,63] ergot alkaloids,[64-67] and alcohol.[68]

Experimental studies have suggested that platelets and their products play a role in altering coronary vascular tone. Thromboxane A_2, a prostaglandin-like substance released from aggregating platelets, has been shown in isolated coronary artery models to provoke coronary smooth muscle vasoconstriction.[69,70] This effect appears to be blocked by the prostaglandin-inhibiting agent indomethacin.[70] In humans, limited clinical studies have suggested that patients with both effort and variant angina have greatly increased levels of thromboxane A_2 degradation products in coronary sinus effluent obtained during spontaneous and provoked episodes of coronary vasospasm.[71] This suggested an increased production of thromboxane A_2 during variant angina and is consistent with the observed increased number of platelet aggregates in coronary sinus blood specimens obtained by Robertson and associates from patients during coronary vasospastic attacks.[72]

Experimental viral infections have produced acute lesions in the myocardium, pericardium, and coronary arteries.[73,74] Administering the vaccinia virus to mice has been shown by Sottnek and colleagues to be associated with an early interaction between virus and blood platelets with consequent peripheral thrombocytopenia.[75] Tomioka and coworkers, using intraperitoneal inoculation of encephalomyocarditis virus, showed extensive formation of platelet thrombi in the heart.[76] In limited clinical studies, intracardiac thrombi have also been recorded in cases of acute viral myocarditis.[9,77-79]

Although only speculative, it can be hypothesized that in the patient presented here, acute viral myocarditis resulted in an early virus-platelet interaction leading to an intracoronary aggregation of platelets, release of vasoactive substances, and consequent coronary artery vasospasm. While the patient was initially given indomethacin, he received only one dose, and therefore one cannot anticipate a significant prostaglandin-inhibiting effect. Other possible pathogenetic mechanisms that might be implicated in this association of viral myocarditis and coronary vasospasm are an altered neurohumoral tone seen in patients with acute heart failure[80] or immunologically mediated coronary vasculitis as has been shown in certain forms of collagen vascular disorders.[81]

While the clinical presentation, electrocardiograms, and response to nitrates and calcium channel blocking agents of this patient are characteristic of variant angina and coronary spasm, no definite angiographic evidence was obtained at the time of the actual chest pain and ST-segment elevation, as these abated rapidly with pharmacologic therapy. Neither was an ergonovine provocation test used in this patient's diagnostic workup, both because of the unknown possible risk of such a procedure in this case[82,83] and the fact that the patient's physicians had decided the clinical picture justified therapy with calcium channel blocking agents regardless of the results of such a diagnostic test whose sensitivity in such cases is unknown. The clinical, ECG, laboratory, and angiographic presentations of this patient, however, strongly suggest intermittent coronary artery vasospasm complicating the initial stages of viral myocarditis.

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Brain Cellular Injury and Recovery—Horizons for Improving Medical Therapies in Stroke and Trauma

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An edited summary of an Interdepartmental Conference arranged by the Department of Medicine of the UCLA School of Medicine, Los Angeles. The Director of Conferences is William M. Pardridge, MD, Professor of Medicine.

After ischemic and traumatic brain injury, many cells may be rendered dysfunctional but are not irreversibly damaged or disrupted. The brain tissue may become metabolically deranged, and neurons, while still alive, are paralyzed and cannot create an action potential or conduct an electrical impulse. This injured brain tissue is in a precarious state of increased vulnerability. If the milieu of the cells is favorable, they may recover; if it is slightly unfavorable, they may die. There is now evidence that reversibly injured brain tissue will die from an ischemic or hypoxic insult ordinarily tolerated by the normal brain. The major challenge of modern research in stroke and trauma is to define the chemical and metabolic milieu in which the injured brain exists and to define an ideal milieu for healing.

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DONALD P. BECKER, MD*: In the past decade there has been an explosion of new information on reversible brain cellular injury. This knowledge promises to provide medical therapies for improving the outcome in stroke and trauma previously unknown or considered impossible. Modern improvements in the treatment of patients with acute traumatic brain injury have significantly improved recovery and shown major reductions in morbidity and mortality. New information about metabolic brain tissue abnormalities, such as brain acidosis and the release of free radicals into brain tissue, provides more opportunities for improving treatment.

In human cases of acute brain injury—from mechanical trauma, ischemic or hypoxic stroke, spontaneous intracranial hemorrhage, compression from tumor or other mass—after the acute event, patients may improve and recover, or they may worsen and die. A new understanding of the mechanisms involved in the evolution of the processes and uncovering the critically involved mechanisms are providing important new insights that will lead to improved medical therapy.

That brain function can be temporarily impaired is an accepted premise. Consider the patient with a cerebral transient ischemic attack from embolus or focal hypoperfusion who has episodes lasting 30 seconds to several minutes of pronounced hemiparesis and then recovers completely. Or the patient who, after a generalized or focal seizure, has a Todd's paralysis that lasts up to 24 hours and then fully recovers. Although the mechanisms involved in these temporary losses of brain function have not been elucidated, they clearly represent a temporary, transient dysfunctional state in brain cells. Most of the tissue recovers completely.[1]

A more complex question relates to understanding the mechanisms of delayed or prolonged recovery after an acute neurologic insult. What happens to brain tissue in a patient who enters a hospital with brain trauma, is unconscious and unresponsive to his or her external or internal environment, and has unilateral decorticate posturing, who during the following weeks progressively awakens and in a matter of months shows major improvement in behavioral and neurologic functions? What factors are involved? The question is whether this represents the following:

- Progressive recovery of injured but not destroyed brain tissue, which lies relatively dormant in a dysfunctional but reversible state—based on the evidence presented later, this probably represents the major mechanism for recovery.
- Reorientation of brain circuitry or relations such that healthy brain tissue takes over the function of destroyed brain tissue—this occurs in young children who can transfer language function from an injured to an uninjured hemisphere; it has not been shown to occur in mature adults.
- Regenerative processes in brain tissue where damaged axons regrow to reestablish synaptic communication, or the ingrowth of uninjured axons occurs to replace vacated synaptic sites on empty dendritic zones—although central nervous system regeneration has been shown to occur in laboratory and clinical human studies, the functional usefulness of

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ABBREVIATIONS USED IN TEXT

CK-BB = creatine kinase brain-specific [isoenzyme]
CSF = cerebrospinal fluid
EEG = electroencephalogram

these new connections is questioned. Recent nervous tissue transplantation studies in mammals suggest that new connections can become functionally useful.[2]

Increased Vulnerability of the Injured Brain

After an acute neurologic injury, the damaged brain tissue is more sensitive to a second injury than is a healthy brain. The damaged brain is operating with impaired metabolic machinery and cannot handle a second injury as well as normal tissue can. A simple experiment recently reported in cats proves this point.

After a mild concussive brain injury, which causes transient electroencephalographic (EEG) changes at impact, followed by a full EEG recovery in an hour and complete neurologic recovery of the animal at 24 hours, the cortex of the suprasylvian gyrus appears normal under light microscopy at 24 hours (Figure 1). After seven minutes of incomplete ischemia—95% reduction of brain blood flow—during which the EEG becomes isoelectric and then recovers several minutes after reperfusion, at sacrifice at 24 hours, the suprasylvian cortex again seems normal (Figure 2). When the normally recoverable insults of trauma and ischemia are administered sequentially, however—a reversible traumatic insult followed an hour later by the ischemic injury—the EEG, which recovers after the trauma, goes flat after the ischemic insult and does not recover with reperfusion of up to 24 hours. At sacrifice, the suprasylvian gyral cortex shows multiple dark, shrunken neurons indicating cellular death, accompanied by perineuronal and perivascular swelling (Figure 3).[3] Ishge and co-workers have recently shown the same kind of increased vulnerability to sequential hypoxic brain damage.[4]

From these observations, two important conclusions can be reached. First, injured brain tissue subjected to a second insult of ischemia or hypoxia, ordinarily well tolerated, may be devastated by this second injury. This is a clinically significant fact because second insults to an injured brain are a common occurrence, are correlated with a poorer patient outcome, and are potentially preventable. In a study by Miller and Becker,[5] 37% of patients suffering severe brain trauma had a partial pressure of arterial oxygen of less than 65 torr, and 15% were hypotensive, having a systolic arterial blood pressure of less than 90 torr (Table 1). A patient who suffers a moderate diffuse ischemic brain injury from arterial hypotension due to myocardial insufficiency may be devas-

TABLE 1.—*Systemic Insults Noted on Admission of 225 Consecutive Patients With Severe Brain Trauma**†

Systemic Insult	*Patients, No.*	*Patients, %*	*Associated With MVA, %*	*Poor Outcome,‡ %*
Arterial hypoxemia—$Po_2 < 60$ torr	78	37	76	59§
Arterial hypotension—systolic BP < 90 torr	34	16	91	65§
Anemia—hematocrit < 30%	21	10	77	62
Arterial hypercarbia—$Pco_2 > 45$ torr	18	8	72	78§
None	117	52	73	35

BP = blood pressure, MVA = motor-vehicle accident, Pco_2 = partial carbon dioxide pressure, Po_2 = partial oxygen pressure

*From Miller and Becker.[5]
†Some patients had more than one insult.
‡Poor outcome includes severe disability, vegetative state, and death.
§Difference from the 35% "no insult" figure is significant, $P < .01$.

Figure 1.—The photomicrograph of cortex of the suprasylvian gyrus in a cat shows that animals subjected to moderate mechanical injury had normal structural cortex at 24 hours after injury (original magnification × 125).

Figure 2.—The photomicrograph of the same area as in Figure 1 shows that cats subjected to 95% reduction in cerebral blood flow had complete structural preservation of cortex at 24 hours after the ischemic insult (original magnification × 125).

Figure 3.—The photomicrograph of a section of cortex of the suprasylvian gyrus in a cat shows that when normally reversible insults of trauma and ischemia are sequentially combined, severe structural changes are observed suggesting that even mild trauma renders the brain more vulnerable to ischemic insults (original magnification × 125).

tated by the delayed recognition of a second attack of hypotension, ordinarily reasonably tolerated.

The second important conclusion is that an injured brain, even one that suffers a moderate concussion or diffuse transient reversible ischemic insult, is in a metabolically abnormal state; the cells cannot handle the metabolic challenge of a second insult. Several laboratory and clinical studies recently conducted have begun to provide preliminary understanding of some of the abnormalities.

Acidosis and Lactate Accumulation in the Injured Brain

Cerebral acidosis occurs in humans after mechanical brain injury and during ischemic brain injury. Since Glaser first described increased levels of lactate in cerebrospinal fluid (CSF) in 1926,[6] several studies on CSF lactate accumulation after head injury have been reported, and most have assessed the prognostic value of CSF lactate levels.[7-15] High and progressively increasing lactate levels have been associated with a poor outcome. The lactate accumulation is intimately associated with the extent and location of brain injury. These changes in lactate concentration signify increased lactic acid production, which may be mainly responsible for the changes in brain pH and cerebrospinal fluid seen after injury.[16] And, indeed, the CSF pH characteristically falls after a brain injury, and the degree of fall is associated with the severity of injury.[17-19]

Cerebrospinal fluid is in communication with, and reflects changes in, brain extracellular fluid.[20(p44)] Extracellular edema fluid is thought to collect in the CSF by diffusion and bulk flow.[21-23] For lactate to appear in CSF, the clearance must be associated to some degree with the kinetics of fluid movement through brain tissue and the processes that govern flow from the brain into the CSF. Reulen and associates have shown that the clearance of edema by the ventricular CSF is a function of the ventricular pressure.[24] A low intracranial pressure would enhance fluid movement and hence the flow of lactate from brain to CSF. Marmarou and colleagues have reported that brain tissue is easily distended by the edema fluid and white matter must reach a level of saturation before fluid enters the ventricles.[25] These findings suggest that the clearance of lactate into CSF by the injured brain will be decreased when the intracranial pressure is elevated. Moreover, it would imply that because of the ability of the tissue to store the fluid, small changes in CSF pH may reflect large stores of tissue lactate.

Although blood in the spinal fluid will produce lactic acid, lactate elevations after brain injury primarily come from the brain itself.[18] In experiments, when blood is shed into the subarachnoid space, CSF lactate levels increase for five to six hours and then begin to fall off. With an acute intracerebral lesion, CSF lactate continues to rise and stays elevated after six hours.[26-28] In patients with a head injury, lactate levels may continue to rise even several days after injury in patients with more severe brain damage.[19]

The normal pH of the CSF is in the range of 7.32 ± 0.01 and is remarkably constant even in the presence of considerable systemic acid-base disturbances.[28-32] In cases of head injury, the pH of the CSF has been noted to drop as low as 7.269 ± 0.018 in patients in coma associated with decerebrate posturing and below 7.2 in patients with extensive injury, who ultimately die.[14,19] Even though the inherent buffering capacity of CSF is small when compared with blood, a high level of brain extracellular fluid acidosis can be expected to have occurred if the CSF pH is to be significantly lowered by a brain injury.[33,34] This is because the CSF reservoir is large (about 150 ml in humans) and the fluid is constantly being turned over and replaced at a rate of 500 ml per day. Patients with head injuries often have an arterial blood pH in the alkalotic range due to hyperventilation (spontaneous or iatrogenic). If the lowered pH of the CSF is due primarily to the addition of brain extracellular fluid, one can easily imagine extracellular fluid pH values well below 7.0. If ischemia is superimposed, the intracellular pH could theoretically fall to around 6.5 or below.[35-39] The exact level of intracellular and extracellular pH, which can lead to reversible or irreversible cellular injury, has yet to be determined.[40] Acid metabolites other than lactic acid may well accumulate after brain injury. Some experimental studies have shown a discrepancy between the excess CSF lactate accumulation and the associated CSF-bicarbonate reduction, suggesting the presence of additional, unidentified acid metabolites.[27,41]

Severe Cellular Acidosis From Brain Injury—A Cause of Additional Brain Damage?

Myers specifically advanced the hypothesis in 1979 that severe cellular acidosis from brain injury may be the chief cause of additional secondary or delayed brain damage.[42,43] In vitro studies in 1961 by Friede and Van Houten[44] and in vivo studies by Myers and Yamaguchi[45,46] indicated a deleterious effect on brain tissue of excessive tissue lactic acidosis. This led Myers to propose that the occurrence, degree, and distribution of brain injury resulting from hypoxia are determined by the accumulation of lactic acid in brain tissue. He presented evidence that when lactic acid accumulates at high concentrations—greater than 20 μmol per gram of tissue—tissue changes develop that lead to altered cell membrane structure and function, to a breakdown of the blood-brain barrier, to brain edema, and to widespread injury to brain tissue.[42] Lactic acid accumulation is quantitatively related to the carbohydrate concentration in the brain during a hypoxic or ischemic insult. The influence of increased blood and brain glucose levels on the degree of brain injury was discovered by Myers and Yamaguchi[45,46] and has been confirmed since then in studies by Pulsinelli and Petito[40] and Diemer and Siemkowicz.[47]

Studies by Rehncrona and associates[38] and Kalimo and co-workers[49] have established the important influence of severe brain lactic acidosis in the ischemic brain and its detrimental effect on postischemic recovery.[36-38,48] Increased lactic acidosis occurred in animals with hyperglycemia; by varying tissue lactate levels, recovery of the energy state and neurophysiologic variables was not only altered, but the degree of impairment was related to the level of lactate accumulation. Because lactic acid production is associated with hydrogen ion generation, a likely mechanism of the loss of neurophysiologic function and impairment of the energy state recovery is deranged intracellular pH homeostasis. This derangement may seriously affect many reactions and enzyme systems, the integrity of which is necessary for cellular viability.

The effect of lactic acidosis on normal versus abnormal cells—where lactic acidosis accumulates because of the abnormality of the biochemical machinery—may be quite different; for example, the insult survived by healthy tissue may be fatal in damaged tissue. Another factor is that normal

tissue has mechanisms that limit lactic acid production as the pH declines. These feedback mechanisms may not be functional in damaged cells.

Yang and colleagues have recently reported the accumulation of lactate in brain tissue after only moderate brain injury (Figure 4).[50] They postulated that the lactate accumulation is due to impaired mitochondrial function where aerobic metabolism normally takes place. The injured cells may be metabolizing glucose anaerobically, producing less high-energy phosphate, which could partly explain the increased vulnerability state. DeSalles and co-workers recently reported that lactate accumulation continues in the brain-spinal fluid for days after severe brain injury.[51] The level of lactate in cerebrospinal fluid correlates with the outcome (Figure 5).[6]

Rabow and associates recently studied the posttraumatic creatine kinase brain-specific isoenzyme (CK-BB isoenzyme) and lactate concentration activity in cerebrospinal fluid in 29 patients with severe head injuries.[52] The CK-BB isoenzyme activity reached its maximum a few hours after trauma and had a monoexponential drop with a half-life (τ½) of about ten hours, whereas the CSF lactate concentration continued to rise in patients with a poor outcome and decreased only slowly and inconsistently in most of the other patients. This, together with the fact that intracranial pressure problems in the posttraumatic course showed no correlation with CSF lactate levels during the first 24 hours after trauma but were significantly correlated with maximum CK-BB activity, indicates that lactate increase in the cerebrospinal fluid is not, like the CK-BB isoenzyme, a direct, one-stage consequence of the trauma but is due to a continuous production from a derangement of metabolism caused by the trauma. Because even higher CSF lactate levels were survived when not caused by the head injury, and because no significant pH changes were related to the CSF lactic acidosis in these patients when they were ventilated, CSF lactic acidosis is therefore indicative of a severe, although not necessarily intractable, disturbance of brain function associated with intracellular lactate production and acidosis.

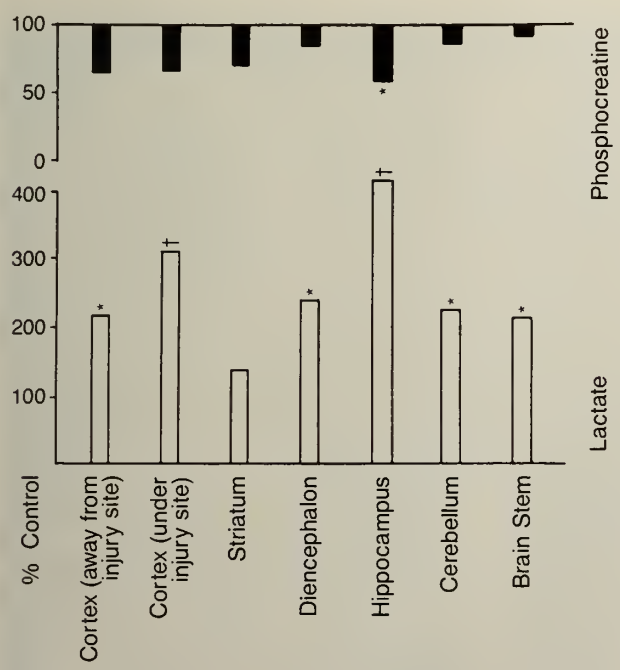

Figure 4.—The graphs show the percentage changes in lactate and phosphocreatine levels from control values noted in uninjured control cats calculated for different brain regions 1 hour after a 2.0-atm fluid-percussion injury. Statistically significant differences are $*P<.005$; $\dagger P<.01$.

Arachidonic Acid Release, Prostaglandin Synthesis, and Release of Oxygen Free Radicals in Brain Injury

Ellis and colleagues have shown the release of arachidonic acid after a brain injury.[53] The brain makes both lipoxygenase and cyclooxygenase enzyme products from arachidonic acid. Free radicals are released during the cascade that can cause anatomic damage to cerebrovascular endothelium and impair normal carbon dioxide reactivity (Figure 6). The damage to CO_2 reactivity can be prevented by prostaglandin synthesis inhibitors and administering free radical scavengers, such as superoxide dismutase, nitroblue tetrazolium, or mannitol (Figures 7 and 8).

Kontos and co-workers showed the appearance of superoxide anion radicals in the cerebral extracellular space

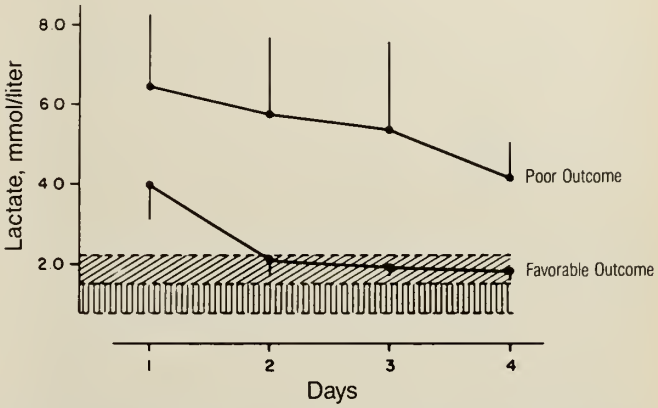

Figure 5.—Lactate levels in cerebrospinal fluid in patients with severe brain injury may remain elevated for days after the injury. This is indicative of continuous lactate production in brain. High lactate levels are associated with a poor outcome.

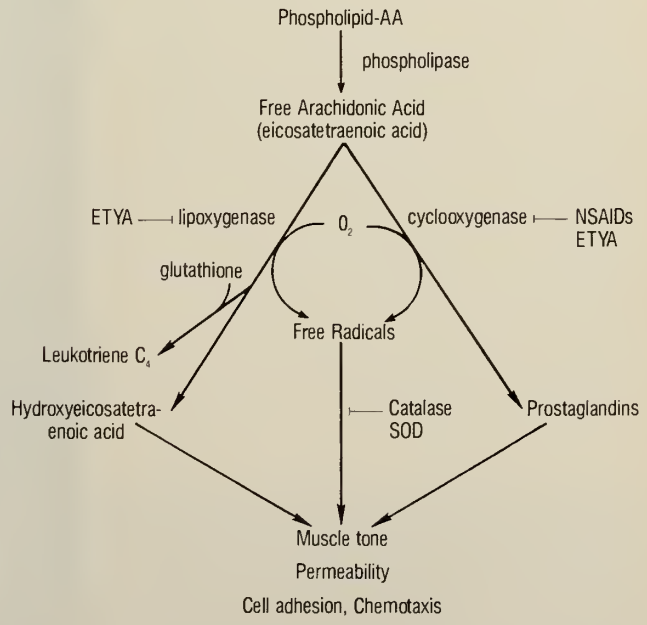

Figure 6.—In cases of brain injury, arachidonic acid is released. This results in a chain of metabolic reactions that result in the production of oxygen free radicals. ETYA = eicosatetraynoic acid, NSAIDs = nonsteroidal anti-inflammatory drugs, SOD = superoxide dismutase

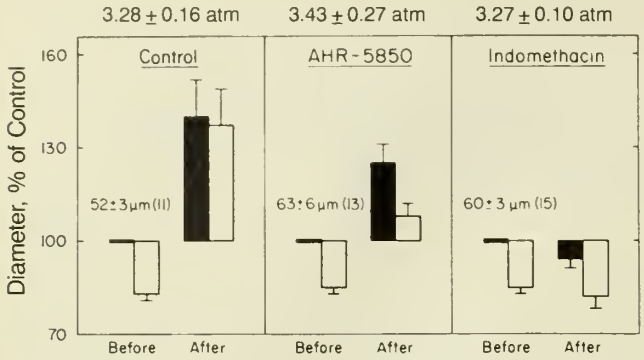

Figure 7.—The graphs show cat cortical arteriolar diameters viewed through a cranial window. With traumatic injury, arterioles dilate, associated with loss of carbon dioxide (control experiment). Prostaglandin synthesis inhibitors (AHR-5850 and indomethacin) given before the injury preserve CO_2 reactivity. The numbers in parentheses are the number of subjects. ■ = normocapnia, □ = hypocapnia

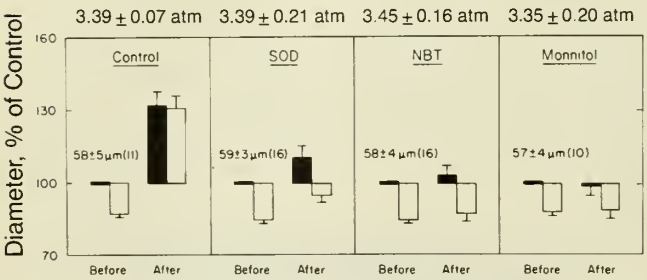

Figure 8.—The graphs again show cats' cortical arteriolar diameters. In this experiment, similar to that in Figure 7, pretreatment with free radical scavengers—superoxide dismutase (SOD), nitroblue tetrazolium (NBT), and mannitol—preserves carbon dioxide responsiveness following percussion injury. The numbers in parentheses are the number of subjects. ■ = normocapnia, □ = hypocapnia

during increased prostaglandin synthesis in cats.[54] When increased prostaglandin synthesis was induced in anesthetized cats equipped with cranial windows by the topical application of arachidonate (200 μg per ml) or bradykinin (20 μg per ml), there was a reduction of nitroblue tetrazolium, resulting in a deposition of the reduced insoluble form of this dye on the brain surface. The amount of reduced nitroblue tetrazolium was measured spectrophotometrically after the brain was fixated by perfusing with aldehydes to eliminate interference from hemoglobin. The topical application of 56 units per ml of superoxide dismutase or 20 μg per ml of indomethacin inhibited nitroblue tetrazolium reduction by 76.5% to 82.5% and 78% to 85.5%, respectively. These results show that most of the nitroblue tetrazolium reduction was accounted for by a superoxide anion radical generated in the course of arachidonate metabolism through the cyclooxygenase pathway. No superoxide production could be detected in the absence of arachidonate or bradykinin. Histologic examination showed no evidence of parenchymal cellular damage or vascular damage and no accumulation of leukocytes. Pronounced leukocyte accumulation occurred 24 hours after topical arachidonate application in rabbits with permanently implanted cranial windows. The superoxide appearance was reduced severely by administering 4,4′-diisothiocyano-2,2′-stilbene disulfonate and phenylglyoxal, two specific inhibitors of the anion channel. The most likely explanation for these findings is that increased metabolism of exogenous or endogenous arachidonate through cyclooxygenase results in the appearance of a superoxide anion radical in the cerebral extracellular space. Superoxide crosses the membrane of undamaged cells by the anion channel.[55]

Release of the superoxide anion radical and other yet-to-be-defined toxins into the extracellular space by partially damaged tissue, or from blood or disrupted brain tissue, could permanently damage cells ordinarily destined for re-

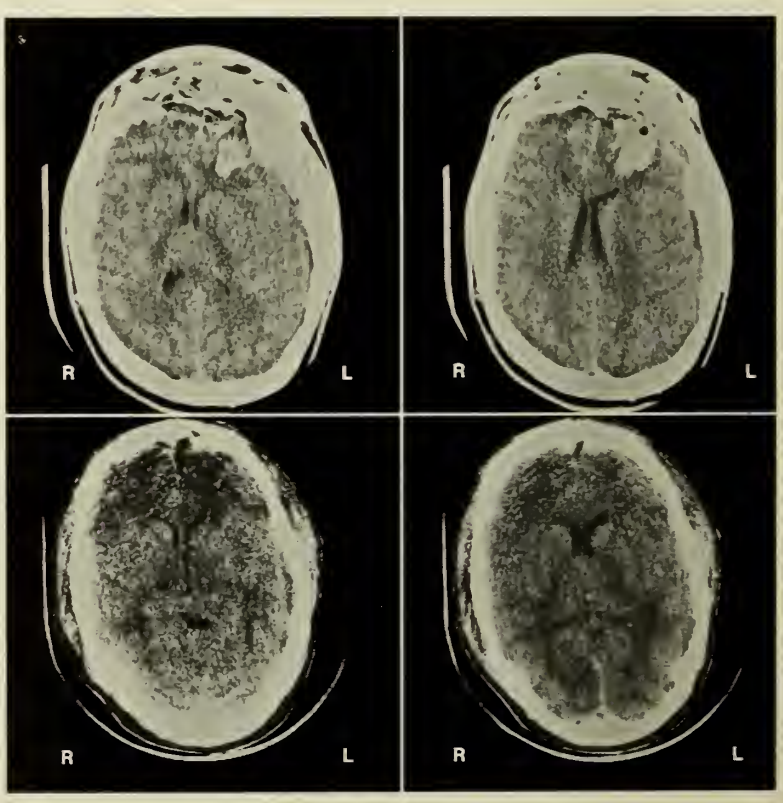

Figure 9.—**Top,** Computed tomographic scans were taken of a 19-year-old UCLA football player who sustained a bifrontal skull fracture and hemorrhagic contusion after a fall. The patient was confused with intermittent lethargy but without focal deficit. He underwent craniotomy with complete resection of hematoma and contused tissue. **Bottom,** Scans taken 5 days postoperatively show mild edema but no evidence of hematoma or hemorrhagic tissue. Clinically the patient did well, returning to school 6 weeks after the operation. The only deficit was anosmia.

covery. This delayed chemical injury may explain the progressive worsening sometimes seen in patients with acute brain injury, even in the absence of impaired cerebral blood flow, an elevated intracranial pressure, or inadequate delivery of nutrients to brain tissue. Even small volumes of blood accumulated in brain tissue may cause diffuse changes in tissue metabolism and a diffuse alteration in the EEG. That blood itself releases chemicals probably damaging to surrounding tissue is a popular hypothesis now being studied in several laboratories.

Two recent cases help explain the point: In one patient who entered hospital with a severe diffuse brain injury, a frontal lobe contusion was removed in two hours after the injury. At five days his computed tomographic scan looked almost normal and he made an excellent recovery (Figure 9). Another young patient was only dazed after falling off a golf cart and striking his head. His frontal lobe contusions were not removed, and at 24 hours after the injury he had gone from sleepy but alert to comatose and decerebrate; the lesions had enlarged remarkably (Figure 10).

The most exciting aspect of the recent discovery of a partial cellular injury associated with metabolic dysfunction is that it promises the early development of new modes of medical treatment. Morbidity and mortality after stroke and trauma can be significantly improved. For example, Newlon and co-workers have shown that half of patients who arrive alive at a hospital after a severe brain trauma die despite their having initial brain electrical activity that is consistent with their making a good recovery.[56] Improved management methods are sorely needed for such patients, as well as those with acute stroke. Dealing directly to reverse biochemical abnormalities and improve metabolic dysfunction may be an important direction of future therapy to improve brain tissue recovery.

TABLE 2.—*Neuropathologic Classifications of Head Injury*

Primary or impact damage	Secondary or complication injury
Cerebral contusions	Diffuse white matter degeneration*
Intracranial hemorrhage	Epilepsy
Diffuse axonal injury	Progressive neurologic disease
Hypoxic brain damage	Substantia nigra depigmentation
Edema	Neurofibrillary tangles
Fat embolism	Concussion

*From Strich.[59]

Cerebral Concussion as Head Trauma—Morphobiochemical Aspects

M. Anthony Verity, MD*: Brain damage resulting from head injury has major socioeconomic effects on society. Significant intellectual, psychological, or personality changes impose financial and mental strains on friends and family.[57] In this conference we shall consider the various forms of brain damage induced by trauma and especially by concussive injury.

Classifications of brain damage resulting from nonmissile-induced head injury encompass clinical pathologic or pathogenetic mechanisms, or both. Unfortunately, the overlaps between various forms of brain injury with the merging of primary and secondary types of injury make it difficult to propose a clear-cut, meaningful classification. We have found a classification based on primary (or impact damage) and secondary (or complication injury) effects to be of value. Primary or impact damage includes both focal and diffuse brain injury. In this classification (Table 2), concussive injury represents a separate clinicopathologic problem.

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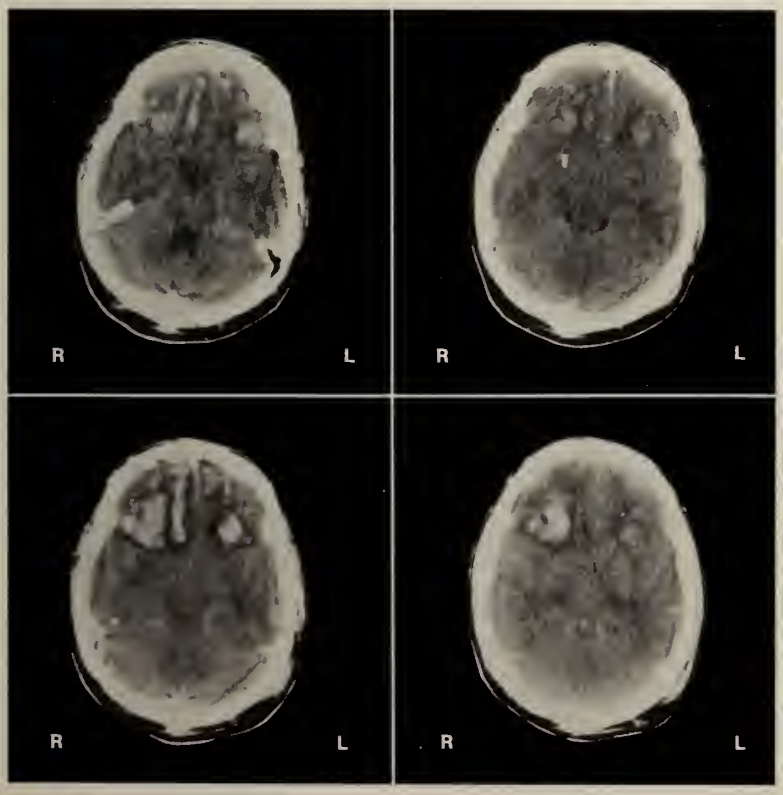

Figure 10.—Top, Computed tomographic (CT) scans were taken of a 23-year-old man struck in the occipital region with resultant bilateral contrecoup lesions. On presentation, the patient was conversant but had deteriorated within 36 hours, becoming obtunded and posturing intermittently. **Bottom,** The CT scans show consolidation and enlargement of hemorrhagic tissue. Management elsewhere included hyperventilation and the administration of steroids without surgery. Shortly after the second scan, the patient had herniation of his brain and died.

Cerebral contusions are punctate or focally confluent hemorrhages, usually at right angles to the cortical surface with emphasis at the crown of the gyrus. These may resolve with appropriate scarring of the gyri, shrinkage, and hemosiderosis; their distribution in the brain is characteristic. The orbital surfaces of the frontal poles, temporal poles, and cortex above and below the sylvian fissure are involved. Intracranial hemorrhage may be extradural, subdural, or intracerebral with variable overlap. The intracerebral hematomas of head injury are often multiple and occur deep within the hemispheres. They result from direct rupture of intrinsic cerebral vessels and may be predicated on preexisting intrinsic vascular disease, especially those associated with accelerated cerebrovascular atherosclerosis or with congophilic angiopathy accompanying presenile dementia.[58]

Since the original description by Strich,[59] the concept of diffuse axonal injury has received strong support from the detailed clinicopathologic studies undertaken by Adams and associates.[60,61] Such diffuse axonal damage is usually identified in the corpus callosum, the rostral brain stem, or as diffuse change throughout the brain. These findings are manifested neuropathologically in the classical retraction balls of Cajal shown in silver-impregnated preparations. In chronic disorders, clusters of microglia throughout the white matter are evident, often associated with wallerian-type degeneration at a distance. Povlishock and colleagues identified axonal retraction balls in cats subjected to minor head injury and found that these changes are not due to axonal rupture but represent a segmental axonopathy followed by segmentation, rupture, and retraction.[62]

The problems of hypoxic brain damage and edema have long been recognized[63] and are often represented as boundary zone hypoxic-ischemic lesions in regions between the major cerebral arterial territories. Arterial spasm is now accepted as occurring after head injury.[64] The pathogenesis of brain swelling, although a major factor in contributing to the raised intracranial pressure, is unclear. Swelling adjacent to contusions may be expected, but diffuse bilateral cerebral hemisphere swelling must relate to increased permeability at a capillary level with loss of physiologic regulation. Povlishock and co-workers found that horseradish peroxidase migrated across the capillary endothelium as a result of increased pinocytosis.[65]

We shall present the morphologic and presumed metabolic basis for concussive brain injury. Since the early investigations of Windle and Groat and colleagues, the term has come to imply a traumatic disruption of the functional integrity of the nervous system with sudden loss of consciousness.[66,67] The role of the brain-stem reticular activating system has been analyzed[68]; this portion of the brain stem is significantly affected, although the structural, biochemical, and electrophysiologic correlations are still not clear. Various pathogenetic mechanisms have been proposed (Table 3).[62,66,69-72] Retrograde degenerative changes have been identified in the neurons of the brain stem after concussion.[66,72,73] The role of the cervical spinal cord in inducing such retrograde neuronal degeneration is still unclear. Various conflicting studies have examined the permeability of brain blood vessels after experimental head injury, especially concussions. Many of these early studies failed to detect changes in vascular permeability.[74,75] More recent studies, however, have shown significant early changes in vascular permeability preferentially located in the brain stem and upper cervical cord, probably accounting for the failure of detection by other investigators.[69,70] Hayes and associates have recently collected data pertaining to the apparent selective involvement of the brain stem and pontomesencephalic area after concussive injury.[71] Using the method of Sokoloff and colleagues,[76] these investigators found that cerebral concussion in the rat promoted reversible behavioral suppression associated with an increased rate of glucose use in the dorsomedial pontine tegmentum. Such increased local glucose use represents a functional activation of this brain-stem region. These recent data are of interest because of the findings by Brown and co-workers, who showed ultrastructural and biochemical evidence for glycogen dysmetabolism in the brain-stem reticular formation after controlled concussive injury in guinea pigs.[72] The polysaccharide accumulated in dendrites, axon terminals, and in variable amounts in astrocyte cytoplasm.

The pathogenesis of such polysaccharide accumulation is unclear, and significant questions remain. What changes in metabolic pathways may be activated to account for the increased accumulation of glycogen? Why does glycogen preferentially accumulate in astroglia in local brain injury? The functional significance of nervous tissue glycogen is still unclear, but it probably serves as an energy reserve for neurons. The predominantly glial localization with an intimate relation of glial processes between neurons and the microvasculature provides a storage reserve capable of being altered in pathologic and disease states.

A key to understanding the metabolic interactions between glial cells and neurons rests in the signals by which such interactions may be controlled. Accumulating evidence highlights the role of potassium in this respect (Table 4).[77-79] Kai-Kai and Pentreath and colleagues have shown a more precise event evoked by the potassium signal[80,81]; they used the finding that radioactively labeled 2-deoxyglucose is selectively incorporated into glycogen, which unlike glucose effectively remains trapped within the glycogen. The distribution of labeled 2-deoxyglycogen can be studied by electron

TABLE 3.—*The Pathogenesis of Concussive Injury*

Diffuse axonal injury*
Brain-stem neuron chromatolysis†
Increased vascular permeability with exudation—lateral brain stem‡
Blood-brain barrier increases permeability to PO_4^{-3}§
Cerebral glucose use decline in midbrain (except pontine tegmentum)‖
Glycogen accumulation in brain stem¶

*Povlishock et al.[62] †Windle et al.[66] ‡Rinder and Olsson.[69] §Cassen and Neff.[70] ‖Hayes et al.[71] ¶Brown et al.[72]

TABLE 4.—*Proposed Significance of Extracellular Potassium Concentration in Astrocyte Metabolism*

Restores K^+ levels
Restores other ions (not by activating sodium-potassium pump)
Redistributes K^+
Glial metabolism (tissue culture)
Increased O_2 consumption
Increased glucose uptake
Pyruvate kinase activation
2-Deoxyglucose experiments*

*See text for description.

microscopy. These investigators found that elevated extracellular potassium levels produced an increased incorporation of 2-deoxyglucose into glycogen of glial cells surrounding activated neurons. This study shows that increased neuronal activity causes a potassium-mediated increase in 2-deoxyglucose uptake and incorporation into the glycogen of glial cells. The role of potassium in controlling glycogen metabolism is well established, but it is not known which enzymic loci are potassium dependent. We can thus develop a hypothesis (Figure 11) that after concussive injury, pathologic concentrations of potassium accumulate in the interneuronal-glial interspace, especially around axodendritic and synaptic regions. In this model, the adjacent glial cells see a potassium signal, which stimulates glycogenesis within the glial cell and adjacent synaptic region.

These observations on morphologic and biochemical expressions after a concussive brain injury suggest a mechanism whereby the neuron-glial cell metabolic interaction can be disturbed. We have seen how an abnormal potassium signal may influence glycogen metabolism. The possibility of other interactions relating to a disordered trophic role or abnormal depolarization may be postulated. There is no doubt that the ultimate effect of single or multiple concussive episodes will be to impair the established interactions between neurons and glia. An analysis of such cell-cell interaction will be of value in understanding the pathogenesis of concussive injury and possibly account for the well-recognized postconcussive syndromes of amnesia and dementia.

Axons Injured in Brain Trauma

JOHN POVLISHOCK, PhD*: In the preceding passages, considerable attention has been devoted to the pathophysiology of brain injury, showing cellular, metabolic, and functional changes subsequent to the traumatic episode. The role of axonal damage in dictating the outcome and neurologic state in those patients whose traumatic course has been uncomplicated by mass lesions or secondary insults has been considered. In this context, then, one can appreciate that axonal injury is an important component of head injury and worthy of detailed investigation. Traditionally, axonal injury has been studied by postmortem examination of head-injured humans in whom the presence of enlarged reactive axonal swellings, classically characterized as retraction balls, was considered evidence of traumatically induced axonal damage.[61,82] Such axonal injury has been described in cases of severe, moderate, and even minor head injury, and it was thought that the shear and tensile forces of a traumatic event physically tore axons.[61,82,83] This event caused immediate axonal retraction with the expulsion of an axoplasmic mass forming an enlarged reactive swelling, the retraction ball.[61,82] As this concept of axonal injury implied that head injury elicited an immediate and devastating form of damage resulting in overt axonal discontinuity, the overall inference of this finding was rather grim. Regardless of the skill of a clinician or rigor of the therapeutic approaches, it seemed that nothing could be done to either stabilize or reverse that axonal damage elicited by the immediate, traumatically induced tearing of axons.

In more contemporary studies of head injury using well-controlled animal models of injury, these traditionally held concepts have been rejected, which has necessitated a reevaluation of axonal injury and its clinical ramifications. In our laboratory, we have systematically studied the posttraumatic evolution of reactive axonal change in cats subjected to minor or moderate forms of fluid-percussion brain injury.[62] By assessing the anterograde axonal transport of horseradish peroxidase studied at the light and electron-microscopic levels in these cats, we have found no evidence to support the concept that head injury elicits immediate axonal tearing with reaction ball formation.[62] Rather, we recognized that the compressive or tensile forces, or both, associated with the traumatic episode triggered more subtle yet progressive forms of change. Immediately after trauma, those long tract systems assessed showed no overt disruption; rather, discrete focal abnormalities were seen. Focal axolemmal irregularity was first recognized and, during a three-hour posttraumatic course, this focal change was associated with microtubular clumping and initial organelle pooling, which was linked to an impairment of axoplasmic transport. With continued survival, this focal organelle accumulation progressed; it was associated with axonal lobulation and with the formation of axonal swellings connected by a thinned axonal segment. Ultimately, these swellings separated and thereby caused overt axonal discontinuity. The overlying myelin sheath, when present, then underwent focal separation, collapsing to coalesce and encompass the now-detached proximal and distal axonal swelling. During the next 12 to 24 hours, the proximal swelling increased further in mass and in organelle content because of the impaired axoplasmic transport, resulting in the formation of a reactive swelling (retraction ball) of classical description. The distal detached segment, on the other hand, showed the onset of wallerian degeneration.

These observations made in minor-to-moderate experimental head injuries are of interest from several perspectives. From the clinical aspect, the delayed posttraumatic

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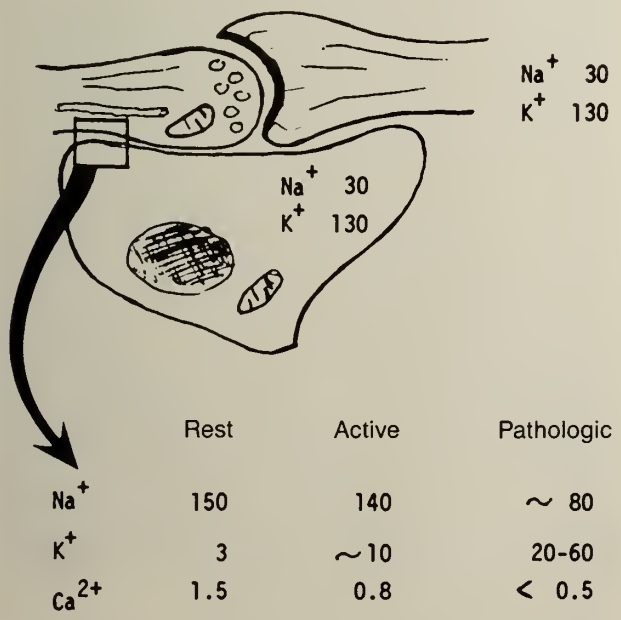

Figure 11.—The values for extracellular concentrations (millimoles per liter) of potassium (K^+), sodium (Na^+), and calcium (Ca^{2+})—represented in the neuronal-glial interspace—are given for the resting or active state and after massive depolarization, for example, postconcussive state. The abnormal values for potassium are sufficient to stimulate glial glycogenesis.

development of axonal separation with eventual reactive swelling implies that there is a time frame after head injury during which potential therapeutic approaches may be capable of either stabilizing or reversing the progress of the above-described axonal changes. Moreover, from the neurobiologic perspective, the subtle progressive temporal development of the reactive axonal swellings poses many questions in regards to their long-term fate. This is of particular interest because such reactive axonal swellings frequently occur in otherwise unaltered brain tissue. The related neuronal somata and dendrites show no abnormality,[84] and comparably the related vasculature manifests no mechanical disruption, alteration in blood-brain barrier status, or reduced regional blood flow.[65,85] Thus, given the relative intactness of the related brain parenchymal microenvironment, one would naturally question whether the traumatically induced swellings would, over time, remain unchanged, degenerate, or mount a regenerative attempt.

To explore this issue, we began to study the fate of traumatically induced reactive axonal swellings over a three-month posttraumatic course.[85,86] Cats were anesthetized and subjected to a fluid-percussion injury.[87] Essentially, such an injury entailed delivering a hydraulic pressure transient to the surface of the intact dura overlying the superior sagittal sinus. The hydraulic pressure caused an elastic deformation of the underlying brain, and the severity of the injury, determined by a transducer, was permitted to range from 1.3 to 2.5 atmospheres during an 18-millisecond period. Such injuries were in the minor-to-moderate range, which resulted in a transient concussive response. After the injury, the animals were permitted to recover and then were evaluated at various time points during a three-month period. Two days before the end of the desired survival period, the animals were reanesthetized and their major cerebral cortical and cerebellar efferents were anterogradely labeled by means of cerebral and cerebellar implants of wheat-germ agglutinin conjugated to horseradish peroxidase gels.[88] We used anterograde peroxidase passage because our previous studies showed this approach most useful in labeling reactive axonal swellings.[62] At the designated period of survival, the animals were anesthetized and perfused with aldehydes. Their brains were removed and sectioned on a vibratome, with adjacent sections being processed for either light-microscopic[89] or electron-microscopic[90] visualization of the peroxidase reaction product within those reactive swellings under investigation.

Within the first week after injury, all animals showed reactive axonal swellings localized within the cerebral peduncles, the brachium conjunctivum, the basilar pons, the red and vestibular nuclei, and the reticular core. Most of these swellings appeared within the first 24 hours after injury and, as such, appeared as organelle-laden masses capping a neurofilamentous core (Figures 12 and 13). Although such relatively unchanged reactive swellings predominated during the first week after trauma, some showed signs of the onset of degenerative change, whereas others showed the initiation of a regenerative attempt (Figure 12). Specifically, some of the swellings showed complex lobulation with neurofilamentous hyperplasia or increased electron density, all of which seemed consistent with retrogressive change. Other swellings, however, showed numerous reactive sprouts that emerged from the swelling proper (Figure 12). The sprouts ranged from 0.5 to 2 microns in diameter and up to 20 microns in length. They contained tubular and vesicular profiles of smooth endoplasmic reticulum and dense core vesicles. Concomitant with the appearance of the sprouts, the reactive swelling proper showed a reduction in size, most likely due to the redirection of its volume into the numerous sprouting neuritic outgrowths.

With continued posttraumatic survival, the above-described variable axonal responses were studied further. By the end of the first month after trauma, unchanged, degenera-

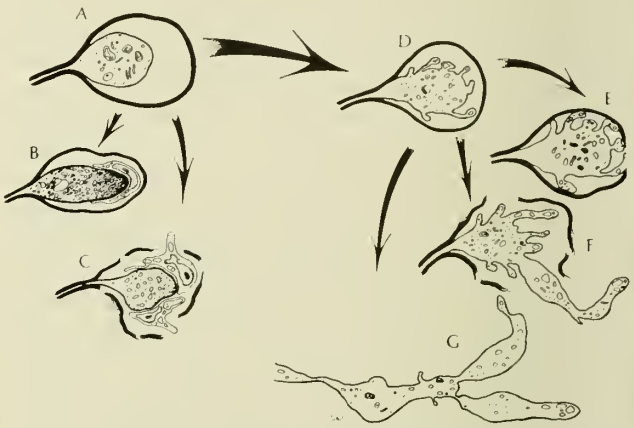

Figure 12.—The diagram shows reactive axonal changes that typically occur within the first month after head injury. Traumatically induced reactive axonal swellings (**A**) can either undergo degenerative change (**B** and **C**) or give rise to a regenerative response, characterized by sprouting (**D** and **E**) and growth cone-like outgrowths (**F** and **G**) (from Povlishock and Kontos[85]).

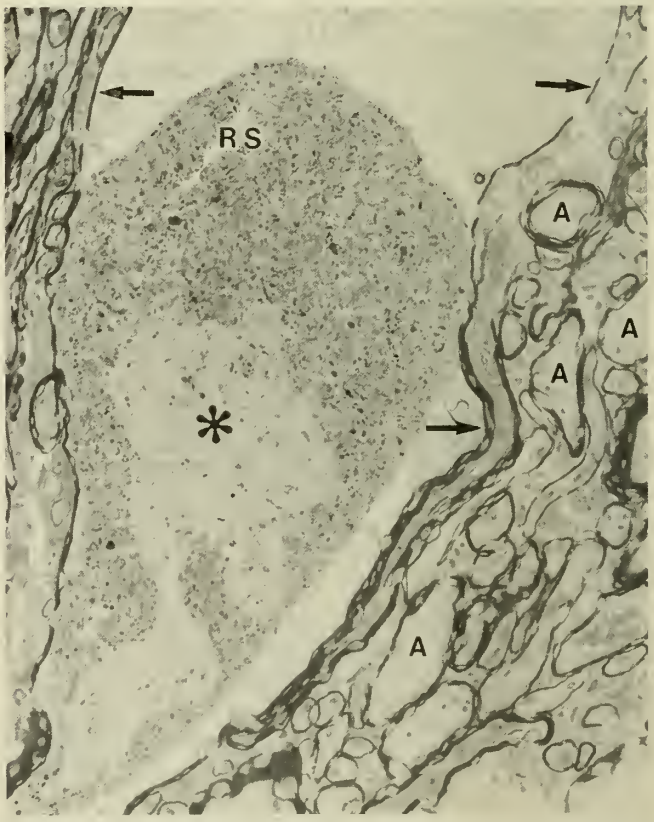

Figure 13.—The electron micrograph shows a reactive axonal swelling (**RS**) 24 hours after injury, with numerous organelles capping a neurofilamentous core (**asterisk**). A thinned, distended myelin sheath (**arrows**) surrounds the swelling. Despite the presence of this reactive axon, numerous surrounding axons (**A**) appear unremarkable (original magnification × 5,000).

tive, and sprouting axonal swellings were found (Figure 14). Degenerative and sprouting swellings now predominated, and these showed continued retrogressive or regenerative change, respectively. Many of the sprout-containing swellings showed continued differentiation, maturation, or both, with the number of total sprouts decreasing as the reactive axonal swelling now gave rise to growth cone-like processes. Such processes were 8 to 10 microns in diameter and up to 100 microns in length. These sprouts and growth cone-like processes frequently paralleled the sides of the overlying distended myelin sheath, and in those cases where the myelin investment was absent, these neuritic outgrowths were recognized to course into the substance of the surrounding unaltered brain-stem parenchyma.

With continued survival during the second and third months after trauma, the above-noted reactive changes were studied further. Both sprouts and growth cone-like processes were consistently found arising from the reactive axonal swellings, which, in general, were considerably reduced in mass as their volume was redirected into such outgrowing processes. In those animals studied during these survival periods, the reactive sprouting and overall regenerative processes showed considerable variation. Even well into the second month after injury, it was not uncommon to see newly sprouting profiles reminiscent of those seen in the early posttraumatic period. Apparently those swellings, which had persisted intact and unchanged during the early posttraumatic period, had now initiated a delayed form of regenerative response. The more mature sprouting and growth cone-containing swellings manifested further change. Overall, the number of sprouts per swelling was reduced. They were, however, longer and seemed to follow the overlying distended myelin sheath in a directed fashion (Figure 15). Such sprouts as well as the growth cone-like processes closely paralleled the distended myelin sheath and usually approximated defects in the myelin sheath, giving rise to the impression that they were entering the substance of the brain-stem parenchyma. In addition to those sprouts originating from the reactive swellings proper, other sprouts arose directly from the axonal shaft proximal to the swelling and from an adjacent node of Ranvier from where they gained easy access to the interstices of the brain parenchyma. We plan to analyze by serial sections the course and potential site of termination of all sprouting and growth cone-like processes.

The above-cited studies reaffirm our initial contention that reactive axonal change is a consistent feature of experimental head injury. Traumatically induced axonal swellings were consistently found, and it seemed that these persisted unchanged, degenerated, or initiated a regenerative response. The degree, manner, and duration of the observed regenerative response are remarkable and are a departure from classical thought regarding the potential for regeneration in the mammalian central nervous system. Although some investigators have advocated the concept of an initial postinjury regenerative response in the central nervous system, this response proved rapidly abortive and never

Figure 14.—The electron micrograph of reactive axonal changes three weeks after injury shows extensive sprouting at the tip of a swelling. One sprout (**curved arrow**) is in direct continuity with the swelling proper (**asterisk**). The other sprouts (**arrows**) in the field contain tubular and vesicular profiles of smooth endoplasmic reticulum and numerous dense core vesicles (original magnification × 30,000).

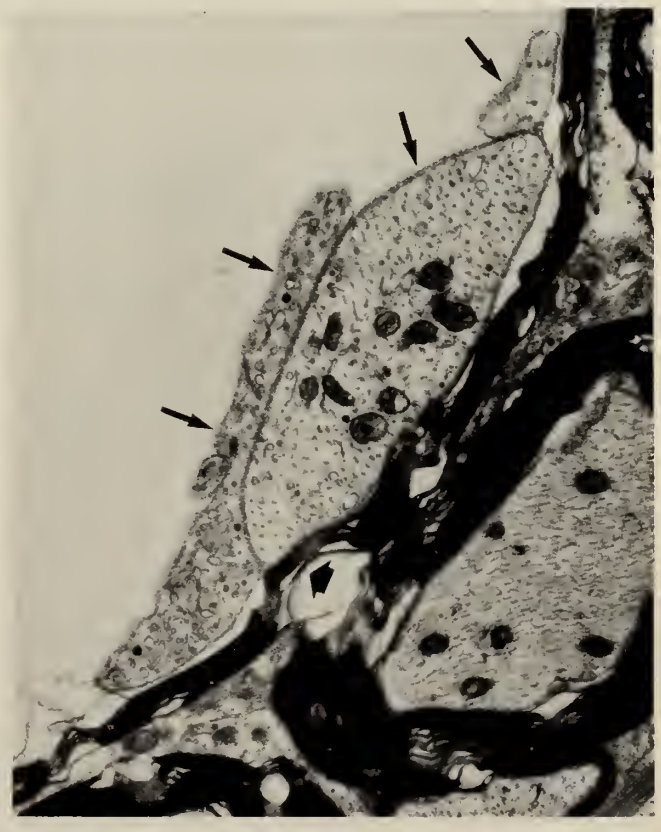

Figure 15.—The electron micrograph shows sprouts and growth cone-like processes (**long arrows**) seen in the second month after trauma. These processes parallel the distended myelin sheath overlying the swelling; defects in the myelin sheath (**block arrow**) suggest that they may serve as conduits for these processes to reach the surrounding brain parenchyma (original magnification × 16,000).

showed the sustained and continually evolving regenerative response seen in this study of head injury.[91,92]

The repertoire of regenerative responses described in the current investigation bears a striking similarity to those responses described in injured peripheral nerves and injured spinal cords of amphibians, who possess a significant regenerative capacity.[93,94] We can only speculate as to why head-injured cats showed such a sustained regenerative response. Perhaps some of those factors unique to minor-to-moderate head injury have contributed to this response. Because such injuries elicit axonal change with the retention of an otherwise unaltered brain parenchyma lacking significant gliosis or vascular insult, it seems conceivable that head injury may have created the ideal microenvironment for any potential regenerative response.

Much remains to be done on this issue. We do not know if with longer survival this regenerative attempt would continue and give rise to directed neuritic growth or rather abort, ending all hope for regeneration. Regardless of the long-term fate of this regenerative attempt, however, the finding of a sustained regenerative response with head injury must be considered intriguing. We may have unwittingly created a unique model for studying potential regeneration of the central nervous system and the effect of various therapeutic regimens.

The direct relevance of these animal studies to humans with head injury is somewhat uncertain. As reactive swellings are also a consistent feature of head injuries in humans, one would predict that changes comparable with those described above also occur in humans, particularly in those patients who have sustained minor-to-moderate injuries and whose course is uncomplicated by mass lesions or ischemia. We are not so naive as to predict that complete and targeted regeneration can occur in humans with head injury; yet, it is conceivable that regenerating processes may form some type of aberrant synaptic contacts that ultimately may permit neurologic improvement.

Biochemical Mechanisms of Cell Injury in Stroke

Glutamate Neurotoxicity in Ischemic Brain Injury

MARSHALL CHEUNG, PhD*: Evidence has accumulated suggesting that neuroexcitatory compounds—for example, glutamate and aspartate—play a major role in the pathophysiology of hypoxic-ischemic brain damage in in vivo and in vitro systems.[95-99] The pattern of cell damage in ischemia seems to coincide with areas of intense glutamate binding[100,101] and high-affinity glutamate uptake.[102,103] Increased neurotransmission mediated by glutamate has been found in the vulnerable regions of the hippocampus.[104] Diemer and co-workers reported that transient cerebral ischemia resulted in a 40% loss of hippocampal CA-1 neurons and suggested a possible neurotoxicity of the glutamate released in this brain region during ischemia.[105] In addition, these putative neurotransmitters have been implicated in the pathologic mechanisms associated with epileptic brain damage,[106] with Huntington's disease,[107,108] and with other neurodegenerative disorders—for example, olivopontocerebellar degeneration[109] and sulfite oxidase deficiency.[110] An elucidation of the role that glutamate and other excitatory neurotransmitters play in cellular injury is therefore important in our understanding of these and other similar brain disorders.

Convincing data are now available to implicate glutamate and possibly aspartate as excitatory transmitters in the mammalian nervous system.[111] They may be responsible for the fast excitatory postsynaptic potentials found in brain and spinal cord neurons.[104] Under normal conditions the extracellular glutamate concentration is kept low by sodium-dependent high-affinity uptake systems present in neurons and glia.[112-114] Under in vivo and in vitro ischemic conditions, however, a massive accumulation of brain extracellular glutamate and aspartate has been documented. The cellular origin of the released glutamate has recently been shown to be glutamatergic neurons.[115] In preliminary experiments, we showed a relatively specific fivefold increase in extracellular glutamate concentrations after in vitro incubation of rat retinas under anoxic conditions (Figure 16).[116] Under these conditions, serine levels increased only 1.5 times.

A similar release of glutamate has been shown in anoxic hippocampal neuronal cultures,[97] cerebellar slices,[96] and rabbit retina preparations.[95,117] With reperfusion or reoxy-

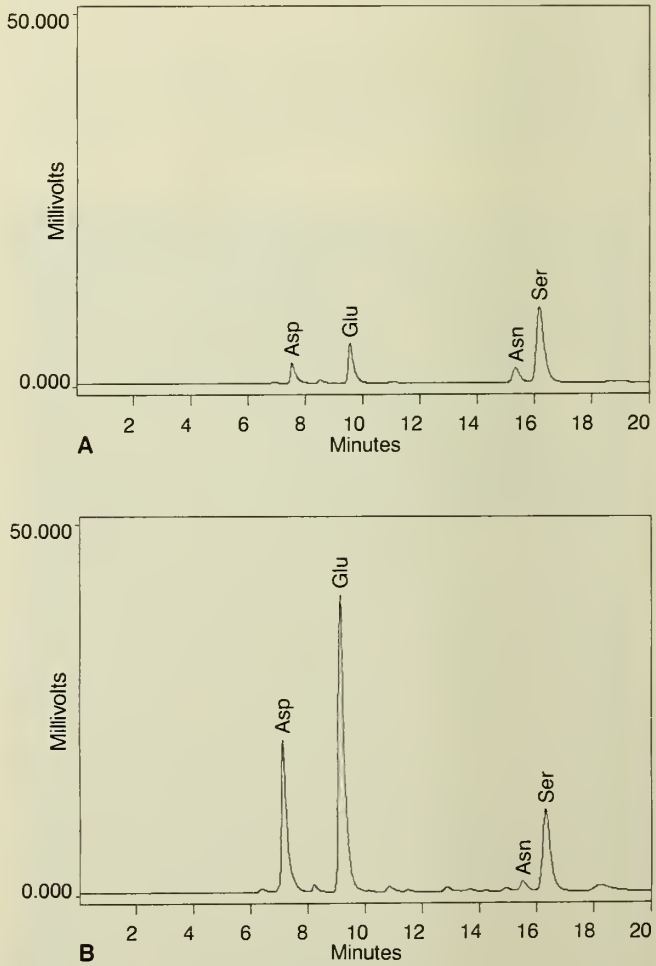

Figure 16.—The graphs show the release of glutamate from rat retina incubated in the presence (**A**) and absence (**B**) of oxygen. The released amino acids are identified by sampling the extracellular medium at 60 minutes. Each sample is collected and clarified before high-performance liquid chromatography analysis according to the protocol for physiologic amino acid analysis described by Jones and Gilligan.[116] Asn = asparagine, Asp = aspartate, Glu = glutamate, Ser = serine

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genation, or both, the increased levels of glutamate returned to normal,[95,117] but extracellular phosphoethanolamine concentrations continued to rise dramatically.[118] In addition, diglyceride levels containing stearate and arachidonate have also been shown to increase after ischemia.[118,119] Although direct evidence is still lacking, the increased levels of these compounds have been suggested to represent ischemia-induced membrane degradation. On the other hand, Dorman and associates[120] proposed an alternative pathway for the phosphoethanolamine liberation in which a loss of adenosine triphosphate during ischemia reverses reactions catalyzed by choline and ethanolamine phosphotransferase (EC 2.7.8.2 and EC 2.7.8.1, respectively) to liberate phosphocholine and phosphoethanolamine from their respective phospholipids.

Although the neurotoxicity of glutamate and aspartate has been known for 30 years, the mechanism of their action has remained elusive. Experimentally adding these neurotransmitters and other dicarboxylic amino acids has been shown to be neurotoxic in vivo and in vitro.[97,110,121] Under anoxic conditions, we found a biphasic effect of glutamate on rat retinal protein synthesis in an in vitro incubation system (Figure 17).[122-124] Stimulation of ^{3}H-phenylalanine incorporation was found at a glutamate concentration of 50 μmol, followed by a dose-dependent inhibition. When the rat retinas were incubated under normoxic conditions, adding glutamate stimulated protein synthesis at all concentrations tested.

Directly adding micromolar concentrations of glutamate also inhibited synaptosomal protein synthesis but only in the absence of magnesium ions (Figure 18).[125] Recent experiments in our laboratory, however, did not confirm the protective effect at 5 mmol Mg^{++}. Because Mg^{++}prevents the presynaptic release of glutamate[126] as well as inhibiting glutamate binding to its postsynaptic receptors,[122] the neurotoxic action of glutamate may be dependent on receptor interactions. The mechanism of cell injury following glutamate-receptor interactions is not known, however. The important relation between neurotransmitter-receptor interactions and membrane phospholipid breakdown (the phosphoinositide cycle) has been reemphasized[127-130] and may provide a mechanism for the neurotoxic action of glutamate. In partial agreement with this possibility, the inhibition of synaptosomal protein synthesis is partially reversed by 5 mmol lithium at higher glutamate concentrations (Figure 19). Lithium has been shown to disrupt the phosphoinositide cycle by inhibiting inositol-1-phosphate phosphatase, thereby preventing the cycling of inositol phosphates to inositol, which becomes rate limiting for the synthesis of membrane phosphatidylinositol.[130]

We hypothesize that, under ischemic conditions, there is a massive release of glutamate, which interacts with target neurons containing specific postsynaptic receptors for glutamate. Because glutamate receptors are not known to be down regulated[95] and sodium-dependent reuptake mechanisms are inactivated during conditions of ischemic energy deficit, there is uncontrolled and persistent neuronal stimulation by

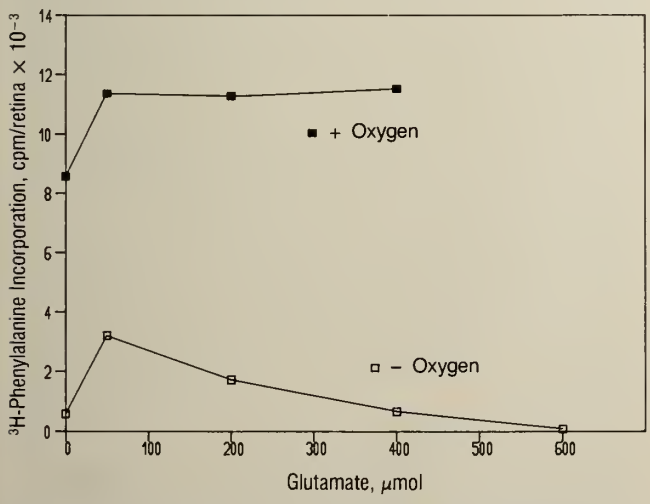

Figure 17.—The graph shows the in vitro effect of glutamate on the synthesis of proteins by rat retina. Rat retinas are incubated in an electrolyte solution described by Ames and Nesbett[122] in the presence and absence of oxygen and varying concentrations of glutamate. The rate of protein synthesis is estimated from the incorporation of ^{3}H-phenylalanine into trichloroacetic acid-insoluble material as described by Verity and colleagues[124] for synaptosomal protein synthesis.

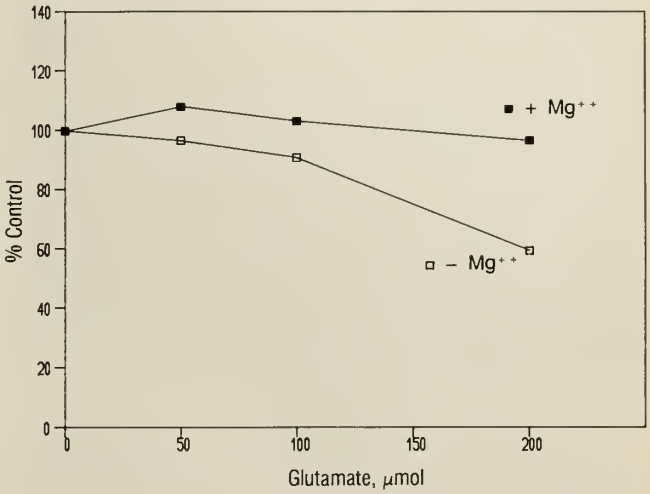

Figure 18.—The graph shows the effects of magnesium on glutamate perturbation of synaptosomal protein synthesis. Synaptosomes were prepared according to the method described by Verity and colleagues.[125] The effect of varying concentrations of glutamate on synaptosomal protein synthesis was monitored in the presence and absence of 10 mmol Mg^{++}.

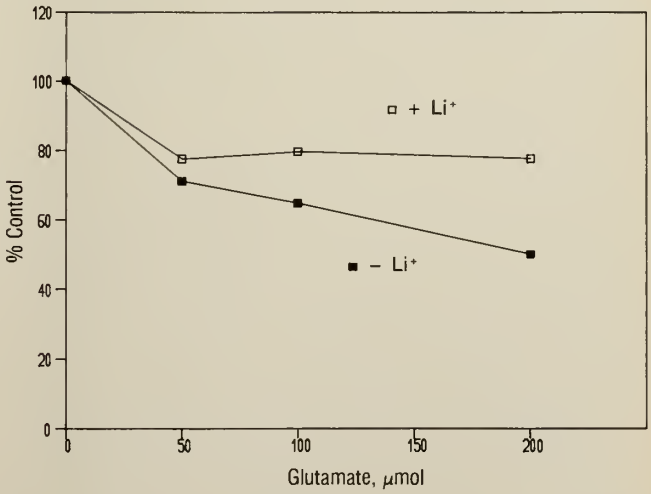

Figure 19.—The graph shows the protective effect of lithium on the glutamate perturbation of synaptosomal protein synthesis. Synaptosomes were prepared according to the method of Verity and colleagues[125] and incubated with varying concentrations of glutamate. In these experiments, incubations were done in a medium containing no Mg^{++} and 5 mmol lithium chloride.

continued glutamate-receptor interactions. Such interactions may abnormally activate the phosphoinositide cycle and perturb calcium homeostasis by stimulating extracellular calcium uptake and mobilizing intracellular calcium from the endoplasmic reticulum.[130] This increase in intracellular calcium levels then stimulates membrane degradation catalyzed by various calcium-dependent phospholipases, for example, phospholipase C and A_2. In addition to promoting membrane degradation and supplying arachidonic acid for the synthesis of eicosanoids, the phosphoinositide cycle stimulates the phosphorylation of a unique set of proteins through protein kinase C.

In cerebral cortex, it has been shown that cholinergic-muscarinic, α-adrenergic, and histamine H_1 receptors are linked to phosphoinositol breakdown. A similar link between glutamate receptor and the phosphoinositide-phosphoinositol cycle has yet to be shown (although recently a new class of glutamate receptor linked to inositol phospholipid metabolism has been reported[131]), nor has the possible role of abnormal activation of the phosphoinositide cycle in cell injury been explored. Brown and co-workers found that 1 mmol glutamate did not stimulate inositol phospholipid breakdown in rat brain cortical slices.[132] Our preliminary demonstration that lithium partially reversed the glutamate inhibition of protein synthesis in rat cortical synaptosomes suggests that such a link is possible but does not fully explain the glutamate effect. Work is in progress in our laboratory to determine the role of glutamate in ischemic cell injury and its relation to the phosphoinositide cycle, calcium mobilization, and membrane phospholipid breakdown.

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Traveler's Diarrhea—The Rule of Ps

FORTUNATELY, TRAVELER'S DIARRHEA IS A PREVENTABLE DISEASE. I recommend what I call the Traveler's Rule of Ps, that is, one should only consume foods and beverages that are peeled, packaged, purified, or piping hot. Most of the enteric organisms that cause diarrhea, as well as polio and hepatitis and so on, occur either in tap water, ice, or fresh fruits and vegetables.

If you can peel the fresh fruit and vegetables, they're safe. So mangos, oranges, bananas, and so on, are perfectly safe, no matter where you are. Grapes or tomatoes, however, unless you're willing to peel them, are not.

Packaged food is almost always safe. There have been occasional horror stories: bottled water in Mexico causing an epidemic of diarrhea, and so on, but this is very, very rare. In fact, if something seems reliably packaged and has a seal and looks like it was commercially done, then virtually everywhere in the world, it is safe to consume.

Purified refers primarily to water; and sterilized, purified water is now available, increasingly, throughout most of the common tourist destinations in Mexico and other parts of the commonly-visited developing world.

Remember, though, that ice can carry germs, too. This is one mistake that travelers make quite commonly. Unless the ice is purified—and it is very hard to get accurate information about this—it is best to stay away from it. Just because you're in a fancy place, a fancy hotel, does not mean that the ice is purified or that the water is safe to drink.

Piping hot is probably the most important thing. By that, I mean that if you eat food that has been cooked *now* and served piping hot *this moment* and not touched by anyone else between the time when it's hot and when you eat it, it is 95% + safe. Now, that's not to say something that was well cooked and has cooled off is safe.

—ROBERT B. BARON, MD

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Medical Staff Conference

Therapeutic Dilemmas in Type II Diabetes Mellitus—Improving and Maintaining β-Cell and Insulin Sensitivity

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs Homer A. Boushey, Professor of Medicine, and David G. Warnock, Associate Professor of Medicine, under the direction of Dr Lloyd H. Smith, Jr, Professor of Medicine and Associate Dean in the School of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, School of Medicine, San Francisco, CA 94143.

RICHARD K. ROOT, MD*: *The dietary and drug therapy for non-insulin-dependent diabetes mellitus seems to be a constant source of controversy, possibly because we seem to have made more progress in learning about the risks and complications of different treatments than in learning about the pathogenesis of the condition. What we have learned about treatment and pathogenesis is nonetheless fascinating, and we are fortunate to have John Karam, MD, Professor of Medicine and Associate Director of the Metabolic Research Unit, here to discuss the therapeutic dilemmas posed by type II diabetes mellitus.*

JOHN H. KARAM, MD†: Non-insulin-dependent diabetes mellitus (NIDDM), or type II diabetes, affects more than 8 million people in the United States and accounts for morbidity and mortality from vascular complications with twice the risk as for age- and sex-matched nondiabetic populations.[1] Unfortunately, the pathogenesis of hyperglycemia in this disorder remains obscure, and perhaps for this reason many questions remain unanswered regarding the advantages and disadvantages between sulfonylurea or insulin treatment in patients with NIDDM. In addition, recent reports documenting the susceptibility of the pancreatic β-cell to becoming desensitized to glucose[2-5] and to develop tachyphylaxis to sulfonylureas in vivo[6] have raised further questions as to the manner in which these pharmacologic agents should be administered to be maximally effective. In this presentation, I will review current concepts concerning the pathogenesis of hyperglycemia in patients with type II diabetes, the effect of obesity in this population, and the use of diet, exercise, sulfonylureas, and insulin in the treatment of this disorder, with a caveat that "desensitization" unfortunately seems to occur with all four of these therapeutic modalities.

Pathogenesis of Hyperglycemia in NIDDM and Its Effects on Insulin Secretion and Action

All investigators generally agree that in patients with NIDDM who have fasting hyperglycemia, there are at least two major defects that contribute to the hyperglycemia: a defective pancreatic β-cell response to glucose[7,8] and an impaired action of insulin on its target tissues.[8,9] Because either one of these defects can secondarily induce as well as aggravate the other defect, considerable speculation has arisen as to whether only one of them is a primary defect or whether they coexist initially in the pathogenesis of NIDDM. Regardless of which defect is the primary one, it has become well established that correcting the hyperglycemia by any means, including diet, sulfonylureas or insulin therapy, can improve the pancreatic β-cell response to glucose[10,11] and the impaired tissue response to insulin.[11] This amelioration of both defects by any of these therapeutic maneuvers has given support to the concept that hyperglycemia itself can directly desensitize the pancreatic β-cell[3,4] and that it can in some way induce peripheral tissue resistance as well.[12] This latter observation has stimulated a reevaluation of traditional concepts that sulfonylurea drugs have a peripheral effect of potentiating insulin action because any glucose-lowering effect from increasing insulin secretion in patients with NIDDM would thereby lower peripheral resistance and enhance insulin action.[13] Evidence that insulin therapy is just as effective as sulfonylurea therapy in reducing peripheral insulin resistance in NIDDM[14] and that sulfonylureas apparently have no therapeutic benefit in patients with type I diabetes in lowering insulin requirements or hyperglycemia[15] further supports the concept that the beneficial effects of sulfonylureas in patients with type II diabetes can be explained by their stimulation of pancreatic β-cells to provide more circulating insulin and thereby reduce hyperglycemia. This improved metabolic control can increase the effect of insulin on its target tissues without the need to invoke a direct effect of sulfonylureas on insulin action in vivo.

Role of Obesity in NIDDM

In most western societies, patients with NIDDM have a high prevalence of associated obesity. When this increased adipose mass is predominantly distributed in the truncal region and particularly within visceral mesenteries and omentum,[16] there is increased resistance to the action of insulin, particularly in hepatocytes. An intriguing hypothesis is based on data showing that an increased flux of fatty acids directed into the portal vein from excessive omental fat may be responsible for this hepatic insulin insensitivity.[16,17]

While a genetic predisposition to obesity has long been postulated in humans, only recently has substantial evidence been provided. Stunkard and co-workers have documented a

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ABBREVIATIONS USED IN TEXT

IGF-II = insulinlike growth factor II
NIDDM = non-insulin-dependent diabetes mellitus
UCSF = University of California, San Francisco

correlation between the weights of 540 adoptees and their biologic parents, but no correlation was evidenced with adopted parents.[18] Moreover, among identical twins, the concordance for obesity was twice as high as in dizygotic twins.[19] Yet it has been well established that providing a wide variety and an abundance of high-caloric "cafeteria food" can induce obesity in rats,[20] suggesting that acquired obesity can readily occur in affluent societies without requiring a specific genetic predisposition. Recent data on a newly discovered protein secreted into the blood of rodents from adipocytes and named "adipsin"[21] indicate that its levels are increased during food deprivation and reduced after glucose infusion. Of interest is its low level in models of genetic obesity such as "obob" and "dbdb" mice and "fafa" rats, but normal levels in an acquired-obesity model, the cafeteria-fed rat. This raises the question as to whether a reduced circulating level of adipsin in a human population could be a marker for a genetic type of obesity in contrast to acquired forms of obesity resulting primarily from ingesting high-calorie foods. Results of future surveys in this area will be of interest particularly because of possible therapeutic implications in genetic models of human obesity in which the absence of circulating adipsin could contribute to a reduced fat mobilization.

The Insulin Receptor and 'Postreceptor' Actions of Insulin

Recent characterization of the insulin receptor as possessing a tyrosine kinase within its β-subunit[22] has not only suggested ways for insulin to exert its effects but also indicates a number of possible defects to account for the postreceptor resistance to insulin in patients with type II diabetes.

The insulin receptor is composed of two pairs of distinct subunits derived from a single protein precursor molecule, and each subunit has a specialized function.[22] The α-subunit has a molecular weight of 130,000 daltons and is the portion of the receptor protruding from the cell surface that binds circulating insulin. The β-subunit is smaller with a molecular weight of 90,000 daltons, lies predominantly inside the cell, and contains an insulin-sensitive protein kinase. Each functioning insulin receptor is composed of two α- and two β-subunits. When insulin binds to the α-subunit, the β-subunit enzyme becomes activated, resulting in the phosphorylation of at least one of its own tyrosine components. This somehow results in the internalization of the insulin-insulin receptor complex. Czech has proposed a model in which this internalized complex promotes a cascade of phosphorylations from its activated kinase region that induces an intracellular compartment of proteins to move to the cell surface.[23] These include the glucose transporter protein, transferrin, the low-density-lipoprotein receptor and the insulinlike growth factor-II (IGF-II) receptor. Movement of these proteins—which are sequestered intracellularly during the postabsorptive period—to the cell surface during feeding can explain the actions of insulin on the transport of glucose and other nutrients in insulin target tissues and in promoting growth by giving circulating IGF-II access to a cell surface receptor.

On the basis of this model, a number of genetic defects distal to the insulin receptor might be postulated to account for "postreceptor" insulin resistance—such as abnormalities of the enzymes responsible for phosphorylation of the glucose transporter protein or a mutation of the glucose transporter itself or in its processing. Moreover, abnormalities of phosphatase enzymes might account for a delay in the normal restoration of the insulin receptor to its surface membrane locus, resulting in more resistance in some patients with NIDDM to the action of insulin.

Controversies Regarding Therapeutic Options in NIDDM

Diet and Exercise

In December 1986, a consensus development conference was convened at the National Institutes of Health to arrive at recommendations for the dietary management of patients with non-insulin-dependent diabetes mellitus.[24,25]

Considerable controversy was apparent regarding the content of such a diet. Some nutritionists expressed a concern that each of the three main foodstuffs—fat, protein, and carbohydrate—could be incriminated as contributing to the vascular complications of diabetes. Thus, when saturated fat intake is reduced as a prudent means of reducing the risk of macrovascular disease, questions arise as to the feasibility of replacing it with either protein or carbohydrate foods.

Brenner and Zatz and associates have suggested that a high-protein content in the diet can be harmful to kidneys and retinas by promoting increased hemodynamic effects on their microvasculature.[26,27] They report that vasodilatory effects of amino acids promote an increased blood flow of retinal vessels and hyperfiltration of renal glomeruli, thereby increasing permeability to macromolecules that contributes to basement membrane thickening and capillary damage.

Reaven, quoted by Kolata,[25] cautioned against replacing fat calories with carbohydrate in the diet because of certain potentially deleterious consequences such as an increase in circulating levels of insulin and triglycerides. He cited an association of hyperinsulinism with an increased risk of heart disease. This could be due to a correlation between hyperinsulinemia and an increase in various risk factors such as hypertension, increased very-low-density-lipoprotein levels, and reduced high-density-lipoprotein levels. Those comments prompted the chair of the planning committee for the consensus conference to note[25] that nutritionists have been placed in a bind when giving diet advice to patients with type II diabetes by the concern that a high-fat diet is bad for the heart, a high-protein diet is bad for the kidneys, and a high-carbohydrate diet may adversely increase cardiovascular risk factors.

Other areas of controversy relating to the content of the diet and addressed by the conference included whether certain carbohydrates such as those in beans or pasta induced less hyperglycemia—that is, have a lower "glycemic index"—than did other complex carbohydrates such as those in potatoes or bread, and, finally, whether purified fiber supplements were beneficial in controlling excursions of blood glucose or reducing hypercholesterolemia.

Dietary Recommendations of the Consensus Conference

The planning committee of the consensus conference admitted that further experimental data are needed before the

controversies about the content of the diet can be resolved. Until more evidence is available, however, they proposed the guidelines shown in Table 1 for the dietary treatment of patients with NIDDM.

The conference reaffirmed the need to restrict dietary fat to less than 30% of total calories, with saturated fat making up less than 10% of the total calories. Carbohydrate diets—up to 50% to 60% of total calories—may include sucrose as a taste additive in mixed meals of patients who are lean and do not have carbohydrate-induced hyperlipidemia as long as the sucrose content is less than 5% of carbohydrate calories. The panel did not recommend calculating specific glycemic indices in the dietary treatment of patients with NIDDM and saw no need to change the standard recommendation that proteins comprise 12% to 20% of the calorie content of the diet in people with normal renal function. They noted that studies claiming that dietary fiber was effective in lessening hyperglycemia and hypercholesterolemia were inconclusive. Furthermore, because high-fiber diets may be less palatable, require substantial changes in traditional food patterns, have effects on other nutrients, and can induce abdominal discomfort, particularly in diabetic patients with gastrointestinal neuropathies, they concluded that it was not advisable to use purified fiber supplements for diabetic therapy.[24] If persons wished to increase the fiber content of their diet, however, the panel felt that food high in soluble fiber might be used to replace some other carbohydrates.

Exercise Recommendations of the Consensus Conference

The panel reviewed recent data that seemed to contradict many commonly held beliefs about exercise as an adjunct to low-calorie diets in achieving weight reduction (Table 1). One study showed that the weight loss and improved glycemic control after 12 weeks of a low-calorie outpatient diet alone was not significantly augmented when a program of supervised exercise was added to the same diet in a matched group of NIDDM patients.[28] The authors surmised that obese patients frequently compensate after supervised exercise while dieting by either eating more, or moving less for the rest of the day—or both. Other studies reviewed by the consensus panel confirmed that when obese people entered an exercise program, they moved less during the remainder of the day, thereby canceling out the extra calories they expended while exercising.[25]

The consensus conference reaffirmed that weight maintenance is the cornerstone of diabetes therapy and advised overweight persons to lose weight and those not yet overweight to avoid becoming obese. The panel recommended moderate exercise as an adjunct to calorie restriction but could justify it more for its effect in preventing heart disease than for its aid in losing weight or reducing blood glucose levels.

Sulfonylurea Therapy

In patients with type II diabetes and chronic hyperglycemia, the pancreatic β-cells lose their initial incremental insulin responses to glucose but generally respond briskly to other β-cell secretagogues.[2,8] We have previously reported that this may not be a defect specific for glucose as seven patients with NIDDM were shown to lose their pancreatic β-cell responses to infusions of tolbutamide when they had sustained therapeutic blood concentrations of a first-generation sulfonylurea, tolazamide,[6] but retained responsiveness to an alternate β-cell secretagogue, glucagon. This state of refractoriness to intravenous tolbutamide stimulation was readily reversed when the sulfonylurea therapy was discontinued and β-cells once again responded to acute stimulation with tolbutamide.[6] An illustrative case of a patient manifesting this phenomenon of tachyphylaxis is described below, and data are shown in Figure 1.

The patient, a 56-year-old obese woman with non-insulin-dependent diabetes mellitus, had progressive hyperglycemia over a course of 20 years. She initially at age 39 did not have diabetes but had exaggerated insulin responses to glucose, attributed to her obesity. After diabetes developed, her pancreatic β-cells became less responsive to glucose but still responded briskly to other secretagogues such as glucagon, arginine, or tolbutamide and to combinations of these secretagogues.

As shown in Figure 1, her loss of an immediate insulin response to tolbutamide given intravenously during three intervals of long-term sulfonylurea therapy with tolazamide, but not during four corresponding intervals of diet therapy only, had relevant implications to the concept of tachyphylaxis, particularly because abrupt insulin release to the intravenous administration of glucagon persisted during long-term sulfonylurea therapy in this patient. Similar findings were observed in seven patients studied while receiving oral sulfonylurea therapy sustained for four weeks or longer (Figure 2). In these patients, whose cases were reported previously,[6] mean peak insulin increments five or ten minutes

TABLE 1.—*National Institutes of Health Consensus Panel Recommendations on Diet and Exercise in Non-Insulin-Dependent Diabetes Mellitus (NIDDM)*

Caloric restriction*	
500-1,000 kcal below daily requirements to promote gradual weight loss	
Nutrient content of diet	
Total fat intake	<30% of total calories
Saturated fat	<10% of total calories
Cholesterol intake	<300 mg per day
Protein intake	12%-20% of total calories†
Carbohydrate intake	50%-60% of total calories‡
Sucrose	Up to 5% of carbohydrate calorie intake in mixed meals
Glycemic indices	Not recommended at this time
Fiber intake	Foods high in soluble fiber may be used to replace other carbohydrates; purified fiber supplements are not recommended
Vitamins and minerals	Diet should be nutritionally complete and satisfy recommended dietary allowances
Exercise	
Effect of exercise on metabolic control in NIDDM is often variable and of small magnitude	
Exercise alone is ineffective for weight reduction unless accompanied by an appropriate diet	
Diet alone may be as effective for weight reduction as diet plus exercise in outpatients	
Exercise appears to have special benefits in reducing coronary heart disease in the general population	
Hazards of certain exercises are greater in patients with diabetes who have insensitive feet or proliferative retinopathy	

*Recommendations for obese patients.
†Patients with renal failure may need less protein.
‡Refers to patients without hypertriglyceridemia.

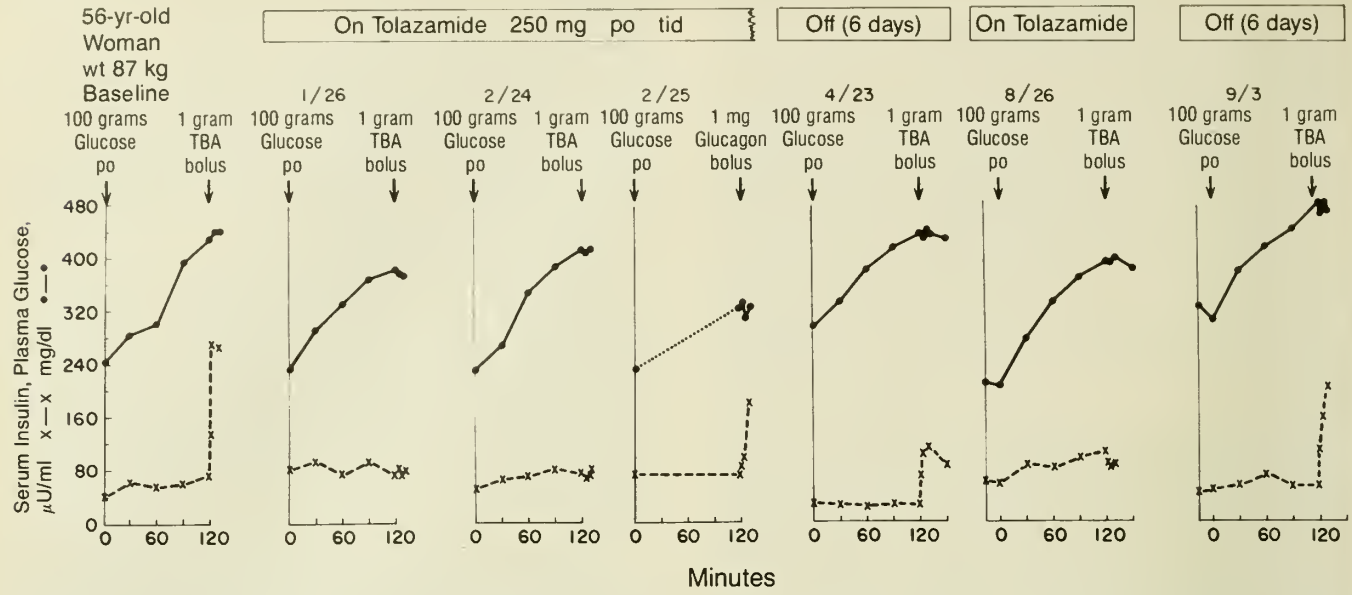

Figure 1.—The graphs show serial pancreatic β-cell stimulation testing with 1 gram tolbutamide (TBA) or 1 mg glucagon given intravenously 2 hours after 100 grams glucose were taken by mouth (po) in an obese woman with non-insulin-dependent diabetes mellitus while she is on or off long-term sulfonylurea therapy (from Karam et al,[6] with permission from the American Diabetes Association, Inc).

after tolazamide was given intravenously were 54 ± 11 μU per ml when not receiving tolazamide but were 0.14 ± 1.3 μU per ml during tolazamide therapy ($P < .001$), even though the serum insulin level rose rapidly after the intravenous administration of glucagon. These results suggest that different signal recognition systems exist on the pancreatic β-cell for various secretagogues such as glucose, tolbutamide, and glucagon, as shown in Figure 3. When exposed to sustained stimulation from chronic hyperglycemia as in NIDDM, the β-cell loses its ability to respond to an abrupt glucose load but retains its responsiveness to intravenous tolbutamide or glucagon. As a sustained level of sulfonylurea stimulation is achieved, the β-cell becomes desensitized to this agent and to glucose but retains its response to an intravenous bolus of glucagon.

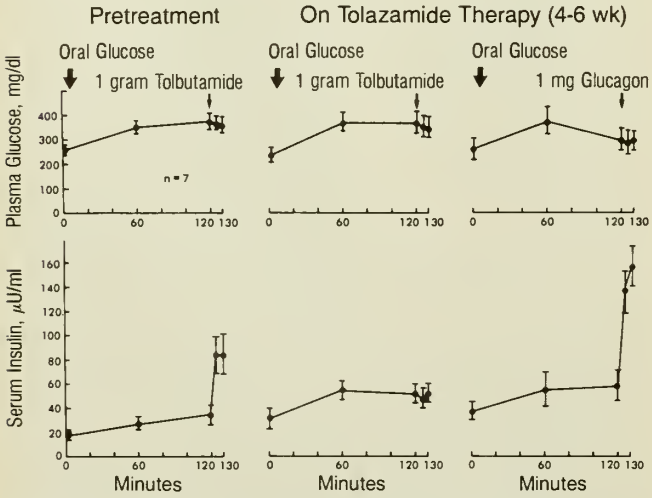

Figure 2.—The graphs show pancreatic β-cell stimulation with 1 gram tolbutamide (n = 7) or 1 mg glucagon (n = 6) given intravenously 2 hours after 50 to 100 grams oral glucose in 7 obese patients with non-insulin-dependent diabetes mellitus while off or on long-term sulfonylurea therapy. Results are expressed as means ± standard error of the mean (from Karam et al,[6] with permission from the American Diabetes Association, Inc).

These findings suggest that a state of tachyphylaxis or desensitization can develop in pancreatic β-cells during their exposure to sustained elevated concentrations of sulfonylureas, and once these sustained concentrations are reduced, the β-cells regain their sensitivity. These data suggest another possible contributing factor to explain the frequency of "secondary failure" to sulfonylurea therapy in NIDDM and suggest greater therapeutic effectiveness if these drugs were administered either intermittently or in "pulse" fashion using sulfonylureas with the shortest duration of action.

Insulin Therapy

More than 40 different pharmaceutic formulations of insulin are available in the United States, differing in concentrations, production method, molecular species, and in the adjuvant used to delay absorption so that action can be prolonged. Because patients with non-insulin-dependent diabetes mellitus are less sensitive to insulin than normal, it seems prudent to prescribe the least immunogenic insulins, such as human insulin, to lessen the induction of additional

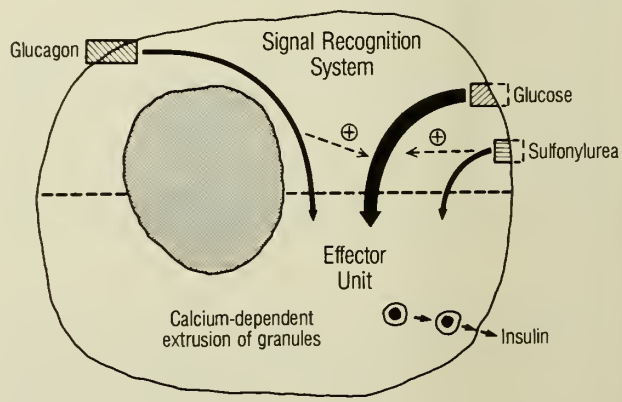

Figure 3.—The schematic diagram of the pancreatic β-cell depicts a model that has distinct signal recognition systems for different insulin secretagogues, which converge on a common pathway by which they discharge insulin.

TABLE 2.—*Available Human Insulin Formulations*

Type of Insulin	*Eli Lilly*	*Squibb-Novo*	*Nordisk-USA*
Regular, crystalline zinc	Humulin R	Novolin R	Velosulin Human
Isophane (NPH) insulin suspension	Humulin N	Novolin N	Insulatard NPH Human
Insulin zinc suspension (lente)	Humulin L	Novolin L	...
Extended insulin zinc suspension (ultralente)	Humulin U	...	...
70% NPH/30% regular	...	Novolin 70:30	Mixtard Human

insulin antagonism in the form of circulating anti-insulin antibodies. Unfortunately, even when pure human insulin is administered from the start of therapy, many patients will acquire some insulin antibodies, presumably because of polymerization of the human insulin at therapeutic dose levels. Human insulin is prepared by either recombinant DNA methods (Humulin [Eli Lilly & Co]) or enzymatic amino acid transpeptidation of pork insulin (Novolin [Squibb-Novo, Inc] or human insulin [Nordisk-USA]). Formulations of human insulin currently available in the United States are shown in Table 2.

Attempts to achieve near-normal glucose levels in obese patients with NIDDM by intensive insulin therapy can result in considerable weight gain. After 36 months of insulin therapy with an implantable pump that maintained normal glycohemoglobins, two obese patients with NIDDM gained 7.5 and 11.2 kg (16 and 25 lb), respectively.[29]

Because both β-cell function and sensitivity to insulin improve after intensive insulin therapy for patients with NIDDM,[11] a decrease in their insulin requirements should be expected as glycohemoglobins become normal.

Conventional insulin therapy using mixtures of regular and intermediate-acting insulin given twice a day is often prescribed. In contrast to lente insulin, NPH insulin does not seem to affect the rapid action profile of admixed regular insulin in vivo,[30] and it is therefore preferred over lente insulin when mixtures are prescribed.

Continually elevated insulin concentrations are known to "down regulate" the insulin receptors,[31] thereby attenuating insulin responsiveness analogous to the way chronic hyperglycemia desensitizes glucose disposal mechanisms[12] in a reversible manner.[11,14] Thus, it may be more effective to lessen hyperinsulinemia by administering insulin in a pulse-like manner using intermittent regular insulin doses, rather than relying primarily on large doses of intermediate-acting insulins. Moreover, insulin administered by nasal spray, if proved safe over the long run, could be of particular benefit in this regard because of the rapid onset but short duration of its biologic action.[32]

Combinations of Insulin and Sulfonylurea Therapy

The possible benefits of prescribing both insulin and sulfonylureas continue to be investigated in clinical trials. A recent review by Genuth of 17 published reports describing combined drug therapy of this type led him to the conclusions given in Table 3.[15] At present there does not seem to be any experimental basis for adding insulin to a regimen of sulfonylureas when the latter drugs are not effective. When this is the case, the use of sulfonylureas should be discontinued and only insulin prescribed. Conversely, when insulin therapy appears to be inadequate, particularly after large doses are being administered, it has been observed that adding sulfonylureas can improve glycemic control.[15]

TABLE 3.—*Combined Insulin and Sulfonylurea Therapy**

- Contraindicated in insulin-dependent diabetes mellitus
- Only modest glycemic improvement in trials of non-insulin-dependent diabetes mellitus (NIDDM), n=11
- No proven long-term advantage in NIDDM
- Current recommendations
  - Add sulfonylureas to therapy regimen of patients with NIDDM who respond poorly to high doses of insulin (>100 U/d)
  - Insulin alone is preferable to combination therapy in patients with NIDDM with failure due to sulfonylureas

*Modified from Genuth.[15]

Therapeutic Perspective

The optimal therapy for type II diabetes mellitus remains elusive in most of these patients for a number of reasons. Foremost is the high prevalence of obesity, which enhances insulin resistance in patients with NIDDM and which, in our affluent society, is so refractory to conventional attempts at weight reduction. In addition, until specific genetic markers for NIDDM become available, the confused heterogeneity of this disorder remains difficult to clarify, thereby hindering the selection of appropriate therapies for particular subgroups. Finally, the well-established pharmacologic concept of tachyphylaxis has recently been reemphasized because of the molecular biologic attempts to define its as-yet-obscure mechanism.[33] Tachyphylaxis and its related concepts of "desensitization," "tolerance," or "down regulation" raise the concern that current conventional regimens of glycemic therapy that provide sustained high concentrations of sulfonylureas or insulin over prolonged periods may reduce the therapeutic effectiveness of these agents. Future clinical trials using "pulse" therapy with shorter-acting sulfonylureas or insulin should help resolve this question. Moreover, resensitizing patients with NIDDM to comply with healthful diet and exercise patterns as well as restoring sensitivity to sulfonylureas or insulin would seem an appropriate goal in the treatment of these hyperglycemic patients with their desensitized pancreatic β-cells, "down-regulated" insulin receptors, and desensitized tissue responsiveness to insulin.

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Epitomes
Important Advances in Clinical Medicine

Ophthalmology

The Scientific Board of the California Medical Association presents the following inventory of items of progress in ophthalmology. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, research workers, or scholars to stay abreast of these items of progress in ophthalmology that have recently achieved a substantial degree of authoritative acceptance, whether in their own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Ophthalmology of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to Division of Scientific and Educational Activities,
California Medical Association, PO Box 7690, San Francisco, CA 94120-7690

Evaluating Vision in Preverbal Children

CHILDHOOD VISION SCREENING has traditionally been done at ages 3 to 5 years, a time when children are finally old enough to tell us what they see. Disorders such as high or unilateral refractive errors, congenital cataracts, and strabismus often go undetected until a preschool vision check uncovers a long-standing loss of vision, or amblyopia. To prevent a permanent loss of vision, amblyopia must be diagnosed and treated early. The American Academy of Pediatrics and the American Academy of Ophthalmology recommend that, in addition to the newborn evaluation, all children have an eye examination by 6 months of age to evaluate visual fixation, ocular alignment, and the presence of eye disease. Children having questionable or unequal fixation responses would be referred for a more precise vision evaluation.

Although formal vision testing in infants and preverbal children has been difficult and often imprecise, the combination of clinical and research techniques currently available permits both early diagnosis and long-term monitoring of amblyopia and its response to therapy. The optokinetic nystagmus response, visual evoked response, preferential looking technique, and fixation pattern responses constitute the primary methods used at this time.

The optokinetic nystagmus response measures pursuit and saccadic movements. Controlling the size of black and white stripes provides an estimation of visual resolution acuity. The visual evoked potential basically records visual responses to stimuli such as checkerboard patterns and light flashes by measuring signals from scalp electrodes placed over the visual cortex. Preferential looking techniques are based on the fact that infants prefer looking at a spatial pattern, usually a grating of black and white stripes, rather than a homogeneous field. Visual acuity information is obtained by observing an infant's behavioral response to looking at grating versus nongrating stimuli as the size of the stripe is varied. Due to technologic, equipment, and personnel factors, the three techniques described are primarily research tools not readily available to most clinicians. The Teller acuity card, a modification of preferential looking developed to provide a rapid clinical technique for measuring infant vision, is now available to practitioners.

Fixation pattern evaluation is the technique used by most pediatric ophthalmologists to assess vision in preverbal children. A child views a target object—toy, picture, or cartoon—binocularly while the strength of the fixation in each eye is compared with the quality of fixation in the opposite eye. The child's general level of fixation is also compared with that expected for a visually normal child of the same age.

Visual acuity determinations can no longer be delayed until children reach preschool age. All children should have an initial vision screening by 6 months of age to detect ocular problems early. Those with possible vision loss should be referred for more complete visual assessment and treatment of amblyopia when present.

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Vision Loss in Pseudotumor Cerebri

BENIGN INTRACRANIAL HYPERTENSION (pseudotumor cerebri) is a misnomer; any disease that produces detectable vision or visual field loss in 49% of patients and severe vision loss (20/200 or less) in 6% to 24% cannot be considered benign. Increased intracranial pressure (pseudotumor cerebri) is a diagnosis of exclusion requiring showing the absence of a space-occupying lesion; a cerebrospinal fluid pressure greater than 200 mm of water, with the fluid chemically and cytologically normal; and normal results on a neurologic examination except for a sixth nerve palsy, vision loss, or a low frequency hearing loss.

Retrospective reviews of patients with pseudotumor cerebri have revealed risk factors for vision loss. Patients showing high-grade or atrophic papilledema, subretinal hemorrhage around the optic disc with or without subretinal neovascularization, a high degree of myopia, anemia, hypertension, and age older than 35 years are at an increased risk of vision loss. Neither the patient's weight, sex, cerebrospinal fluid pressure, nor symptoms of paresthesias, headaches, transient obscurations of vision, diplopia, tinnitus, nor the presence of optociliary shunt vessels are predictive of vision loss.

The primary treatment of pseudotumor cerebri is medical: withdrawal of any offending agents, such as oral contraceptives or tetracycline; weight loss; and the administration of diuretics, carbonic anhydrase inhibitors, and corticosteroids. Many patients are intolerant of or noncompliant with medical management, progressively lose vision, or have persistent headaches on maximally tolerated medical management. Lumbar-peritoneal shunting and optic nerve sheath decompression are surgical alternatives for such patients.

Lumbar-peritoneal shunting, which reduces the elevated cerebrospinal fluid pressure, is indicated for managing nonocular symptoms of pseudotumor cerebri such as headache. Complications of lumbar-peritoneal shunting include shunt failures, low pressure headaches, and pain. Technically, placing a lumbar-peritoneal shunt can be difficult in the typical patient who is obese.

Optic nerve sheath decompression is an effective means of preventing vision loss. Optic nerve sheath decompression requires exposing the optic nerve by a medial orbitotomy and cutting a window or slits in the dural sheath surrounding the optic nerve. Complications of optic nerve sheath decompression, while rare, include ischemic optic neuropathy, diplopia, infection, abnormalities in pupillary function, and orbital hemorrhage. Decompression of the optic nerve is intended to prevent deterioration of vision in the surgically treated eye; therefore, surgery on both eyes is required in many cases. An optic nerve sheath decompression is usually not effective in managing nonocular symptoms such as headache.

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Current Status of Refractive Surgical Techniques

REFRACTIVE SURGICAL TECHNIQUES are designed to improve the accuracy of the eye's focusing system in nearsighted, farsighted, or astigmatic eyes with the goal of eliminating or at least reducing the strength of glasses necessary to correct these conditions. Because the cornea is the eye's most powerful refractive surface—80% of the focusing of parallel light rays is accomplished by the cornea and 20% by the lens—most refractive surgical procedures attempt to modify the curvature of the cornea. The most frequently done refractive surgical techniques are radial and astigmatic keratotomy and epikeratoplasty.

By far the most common refractive surgical procedure is radial keratotomy, where fine microscopic corneal incisions are made in a radial pattern around a central clear zone. This results in corneal flattening, which reduces myopia. Most patients undergoing the procedure now receive 4 to 8 incisions instead of the 16 that were originally recommended.

When radical keratotomy is properly carried out on carefully selected patients, 80% to 90% of patients with low to moderate degrees of myopia can be corrected to 20/40 vision or better without spectacles (uncorrected). Patients with higher degrees of myopia can benefit from a significant reduction of their defect, but only 50% to 70% will achieve 20/40 uncorrected visual acuity. All studies have shown that older patients achieve more effect from radial keratotomy than do younger ones. Most patients who have had radial keratotomy do not achieve uncorrected 20/20 vision, and most of them continue to wear spectacles for activities such as driving.

Common undesirable side effects of radial keratotomy include glare, overcorrection and undercorrection, fluctuations in vision, and difficulties in fitting contact lenses after the operation. Serious complications leading to a permanent loss of vision have been reported but fortunately are rare. A substantial number of ophthalmologists regard radial keratotomy as being in the developmental stage and are not doing the procedure or recommending it. With more refinement, this technique may yield more precise results and few complications, thereby becoming more acceptable and adaptable for widespread use.

Astigmatic keratotomy to correct congenital, postcataract, and post-corneal transplant astigmatism has received increasing attention of late. The incisional patterns have become more standardized thanks to laboratory research, and early clinical reports are promising. The astigmatic corneal incisions are usually transverse and tangential ("T cuts"), rather than radial. Relaxing incisions and wedge restrictions are done in arcuate patterns and are used primarily for post-corneal transplant astigmatism.

In epikeratoplasty, a previously lathed superficial disc of human donor cornea is sutured over a patient's cornea, resulting in a new curvature that is either flatter, steeper, or smoother. Encouraging results have been reported in infants following the surgical excision of congenital cataracts, in children following the surgical excision of traumatic cataracts, in aphakic adults unsuitable for intraocular lens implantation, and in selected patients with keratoconus. The results in highly myopic patients have varied, and epikeratoplasty has not achieved the level of accuracy desired by most refractive surgeons. Considerable regression of the achieved effect has been reported in some patients. Epikeratoplasty for myopia is now being done by a small group of investigators who are refining the original procedure in an attempt to improve its accuracy and stability.

Radial and astigmatic keratotomy and the lathing of epikeratoplasty discs (and possibly even a patient's own cornea) can now be accomplished with potentially greater precision with the excimer laser, and laboratory investigations are currently under way in several centers in the United States and Europe. The possibility of improved accuracy with the excimer laser and the potential to modify corneal wound healing with new pharmacologic agents may improve the accuracy of refractive surgical techniques in the future.

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Assessing Vision in Patients With Alzheimer's Disease

ALZHEIMER'S DISEASE is a disorder of unknown etiology affecting more than 2 million people in the United States. It produces devastating emotional, physical, and financial tolls on patients, their caretakers, and the community in general.

The diagnosis of "probable Alzheimer's disease" can be made clinically, but a histopathologic examination is required to make the definitive diagnosis. A patient generally has progressive memory problems and other cognitive deficits. Visual impairments have also been described, but these have usually been characterized as spatial agnosias and been attributed to deficits of cerebral cortex function. Impairments in contrast sensitivity and in the flash visual evoked potential have been described. Recent histopathologic evidence shows that Alzheimer's disease involves the primary visual pathways. Clinical studies have also found a variety of visual impairments in patients with Alzheimer's disease.

Patients with Alzheimer's disease often complain of difficulties in reading and visual orientation. Because patients with mild disease usually have near-normal Snellen visual acuities and normal-appearing optic nerve heads, however, their symptoms are usually dismissed as nonophthalmic. Studies have shown that although mildly or moderately impaired Alzheimer's patients have normal Snellen acuity, they have deficits in contrast sensitivity functions, visual evoked responses, and eye movement control. Patients with moderate or severe cognitive difficulties are more difficult to evaluate, yet it can be shown that they have the impairments described above to a more serious degree as well as dyschromatopsia and losses in visual acuity. In only the most advanced cases of Alzheimer's disease is optic atrophy noted. Future such studies may lead to the development of a battery of visual tests useful in distinguishing Alzheimer's disease from other common dementias. At present, one has to consider Alzheimer's disease in the differential diagnosis of bilateral optic neuropathy in a patient with dementia.

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Managing Congenital Cataracts

INFANTS, unlike adults, are visually immature. During the first two to four months of life, visual areas within the brain—the lateral geniculate nucleus and the striate cortex—are rapidly developing in response to visual information from the retina. A blurred or distorted retinal image during this critical period can result in abnormal neurologic development and permanent vision loss, clinically known as amblyopia. A cataract large enough to block the pupil will distort the retinal image, thus causing disruption of normal visual development and poor vision due to amblyopia. The presence of a cataract during the neonatal period is an ophthalmic emergency, and a cataract should be surgically removed as soon as possible—that is, within the first few weeks of life.

Modern microsurgical techniques and pediatric anesthesia allow safe and effective early treatment of cataracts. Postoperatively, infants are fitted with extended-wear contact lenses to replace the natural lens removed during the cataract operation. In unilateral cases, the good eye is occluded part of the time to stimulate the vision of the amblyopic eye. Early detection and modern surgical techniques have dramatically improved the previously poor prognosis in these patients. Even infants who are intolerant of contact lenses can now be managed with the use of an epikeratophakic graft. A donor cornea is lathed into the shape of a contact lens and sutured onto the cornea, thus providing a "living" contact lens.

Even with the modern advances, the most important aspect of the management of congenital cataracts is early detection. Neonates should be routinely screened for a normal red reflex. Only through the cooperative effort of pediatricians and ophthalmologists can results be improved in this difficult group of patients.

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Update on Extended-Wear Lenses

THERE HAS BEEN CONSIDERABLE INTEREST in bacterial infections of the cornea associated with extended-wear contact lenses. These lenses are of a higher oxygen permeability that allows them to be worn overnight. Until recently, the lenses were approved for wear for as long as 30 days between removing and cleaning. Clinical experience, however, has shown that some patients can wear these lenses longer than 30 days without difficulty, whereas other patients have problems with overnight wear on a single occasion. A number of reports have noted serious gram-negative infections of the cornea—particularly *Pseudomonas*—occurring in both younger persons who wear the lenses for cosmetic reasons and older persons with aphakia, with the rate of serious eye infections and complications being greater in the aphakic group. Several reports have linked *Acanthamoeba* to serious corneal infections and ulcers occurring in extended-wear lens wearers who wear their lens daily. At higher risk are those who use homemade saline solutions for lens cleaning and those who bathe in nonchlorinated swimming pools and commercial whirlpools while wearing their lenses. Many eyes have been injured, and corneal transplantation needs to be done frequently to rehabilitate such eyes.

Contact lens-induced ulcers occur in about 2% to 7% of patients who use extended-wear lenses for aphakia. The rates are lower in the cosmetic extended-wear group, but the exact incidence is not known at this time. Studies are currently being done that will more clearly delineate the risk of infection in cosmetic wearers of these contact lenses.

There is considerable interest in using gas-permeable rigid lenses for extended-wear use. These are hard lenses that contain either silicone or fluorocarbon to make them more

oxygen permeable. At this point, there is a trend towards the use of gas-permeable hard contact lenses in the extended-wear mode. Early results are encouraging, and certain lenses have been released by the Food and Drug Administration for noninvestigational use. Further experience with these lenses will need to be gained before they can become widely used.

The problems associated with extended-wear contact lenses underscore the importance of patients understanding that contact lenses are a medical device which requires meticulous care. If problems do arise, patients should remove the lenses immediately and seek qualified medical care because delayed treatment is associated with more severe complications.

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Update on Laser Treatment of the Anterior Segment of the Eye

For the past five years, the argon laser has been used in different ways to treat narrow-angle glaucoma and primary open-angle glaucoma. Iridectomy, a time-honored procedure designed to relieve acute angle-closure glaucoma and narrow-angle glaucoma, is now almost exclusively done with the argon and lately with the neodymium-YAG (yttrium-aluminum-garnet) lasers, except for those instances where corneal edema does not allow the laser beam to be effectively directed to the iris.

Argon laser trabeculoplasty was initially extensively done for the relief of uncontrollable primary open-angle glaucoma in patients in whom maximum medication is not controlling the intraocular pressure and there is evidence of visual field loss. The procedure essentially consists of applying argon laser spots at the junction between the pigmented and unpigmented trabeculum over 180 degrees of the trabecular circumference per session. It is done in an outpatient setting, and the patient is not restricted after the operation. The overall results of this procedure were initially encouraging. The reports of five years of follow-up of those patients show that in some, the intraocular pressure tends to rise again. The rate of success of this procedure over five years in one of the recent reports was 50%.

The use of the neodymium-YAG laser is well established for doing posterior capsulotomies after surgically excising a cataract. Basically, the posterior capsule left intact following an extracapsular cataract operation is used as a means of support for posterior chamber intraocular lenses. The posterior capsule may opacify over time, resulting in decreased visual acuity. Before the use of the YAG laser, it was necessary to introduce surgical instruments intraocularly to rupture the capsule. At the present time, the neodymium-YAG laser is used to disrupt the posterior capsule, creating an orifice through which clear vision is again possible. This procedure is done on an outpatient basis and is nonrestrictive postoperatively.

A great deal of attention has recently been devoted to the use of excimer lasers for corneal operations. This group of lasers emits ultraviolet irradiation capable of exciting molecules, forming dimers, and, finally, causing ablation of tissue. The argon fluoride laser emits at 193 nm and is capable of extremely smooth excisions of corneal tissue. A clinical model of this laser has been recently built and has been used to do a refractive surgical procedure similar to radial keratotomy in blind human eyes of volunteer patients.

Another application of the argon fluoride excimer laser essentially consists of reshaping the surface of the cornea to a new curvature, thereby compensating for a refractive abnormality present in the eye. This procedure has been carried out on nonhuman primates and shows promising initial results, although early opacification of the corneas has been reported. Similar procedures have been done on human eyes with infectious corneal ulcers to eliminate the infectious focus, and initial favorable results have been reported (R. Steinert, Harvard Medical School, Boston, and D. Aron-Rosa, Rothschild Institute of Ophthalmology, Paris, oral communications, November 1987). Even though these techniques show a promise in providing more accurate surgical procedures for correcting refractive errors, caution should be exercised, and evaluation of the long-term results in these patients is mandatory.

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Lens Implant for Small-Incision Cataract Operation

There have been numerous technologic advances in surgically excising cataracts that have, in the past several years, made the procedure safer, more predictable, and more visually satisfying to patients. The most important of these developments has been the widespread use of polymethyl methacrylate (PMMA) intraocular lenses rather than aphakic glasses or contact lenses. Another major development has been that of phacoemulsification. With this procedure, a cataract can be removed through a 3-mm incision instead of one about 9 to 10 mm. This can provide better control of wound healing and astigmatic distortion after the operation. To use a conventional intraocular lens after doing phacoemulsification, however, requires enlarging the smaller incision and thus losing the theoretic advantages. To retain those advantages, the intraocular lens must be introduced through a 3-mm opening, which has led to the recent surge of interest in soft or foldable intraocular lenses.

Interest in soft lenses began with hydrogel in the late 1950s, and the first implant was put in a human in 1976. The development of soft intraocular lenses was slow until 1984, when Staar Surgical made the first practical silicone lens implant and popularized its use. Since then, several other manufacturers have produced both silicone and hydrogel lenses, and all of these lenses are being implanted on an investigational basis only. One lens design uses the hard PMMA commonly used for lens implants and "hinges" part of the lens to pass through a 3-mm opening. Another company is working with temperature-sensitive polymers that

can be rolled into a 2-mm tube that unrolls and rehardens inside the eye at body temperature.

These new intraocular lens developments have caused an increased interest in and the use of phacoemulsification for cataract removal. In addition, early reports would seem to indicate that the hydrogel and silicone lenses have similar complication rates to the standard PMMA intraocular lenses. These small-incision implants may have substantial future uses in the surgical treatment of cataracts, but long-term evaluation of their safety is needed. Both types of lenses are still in an investigational stage and, at present, the experience with silicone lenses is limited, with less than five years of follow-up, while knowledge of hydrogel lenses in patients is limited to just over ten years. Hence, more time is needed before these lenses can be shown to have the proven safety and efficacy of the existing standard PMMA lenses.

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Pneumatic Retinopexy

THE USE OF TRANSCONJUNCTIVAL CRYOPEXY and intravitreal gas injection (pneumatic retinopexy) in the office setting for simple rhegmatogenous retinal detachments with retinal tears in the superior retina (8 o'clock to 4 o'clock positions) has recently been proposed. This technique replaces standard scleral buckling, which requires an operating room. The localization of all the retinal holes is important for the placement of transconjunctival cryopexy and for postoperative head positioning. The expandable gas used for internal tamponade of the retinal holes is either sulfur hexafluoride (SF_6) or perfluoropropane (C_3F_8). Because of the differences in lipid solubility of these gases, the duration of the intraocular bubble will vary from 5 to 7 days for SF_6 to 14 to 21 days for C_3F_8. Patients are required to maintain head positioning for several days after the operation or longer at home to allow maximum apposition of the gas bubble to seal the tear(s). For multiple tears, several positions may be required during each day. An arrow may be drawn with a felt-tip marker on the eye patch, or even on the forehead, to assist the patient and family in proper head positioning.

The risk of the procedure includes extension of the retinal detachment into the macula, development of new retinal breaks at a site remote from the original break(s), and intraocular infection—endophthalmitis. In a review of 100 consecutive cases, 84% were attached at six months, with the pneumoretinopexy failures surgically repaired by conventional scleral buckling, improving the overall success rate to 98%. Failure was caused by excessive retinal scarring and new or missed retinal breaks. Pneumatic retinopexy offers advantages in the management of uncomplicated superior rhegmatogenous retinal detachments.

This outpatient procedure reduces the morbidity of hospital stays, general anesthesia, and periocular trauma, resulting in an acceptable reattachment rate with no loss of ultimate anatomic success if a subsequent conventional scleral buckling is required. A careful preoperative examination to determine the presence of all retinal breaks, especially those in the inferior retina, and patient compliance with head positioning after the operation are the major factors in achieving anatomic success.

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Editorials

Physicians as 'Double Agents'

In a recent column in *American Medical News*, Harry Schwartz pointed out that physicians were being forced more and more to become what amounts to "double agents" in patient care, with all that this implies. A double agent in the world of international intrigue agrees to work on behalf of two masters who have conflicting goals and purposes. Often, neither is aware of the agent's responsibility to the other. In addition, it is sometimes necessary for double agents to act on behalf of only themselves, for their own well-being or even survival. The role of a double agent has to be an uncomfortable one, especially for physicians. By definition a double agent can hardly be loyal to both masters and perhaps to neither of them, and, in any event, loyalty to oneself may sometimes become paramount.

Many physicians—and there are more each day—are finding themselves in this uncomfortable role. On the one hand, patients and the public expect them to work fully on behalf of those patients who seek their help, while at the same time they are being pressured more and more to serve as agents of government and others who are trying to reduce the amount and cost of services that are purchased by third parties for patients. This unwanted dual role is already causing serious discomfort for many physicians, who, caught in what seems like an ever-tightening vise, must also try to protect their own personal moral integrity and sometimes their own economic survival. If nothing is done, all this can only get worse as the demand for services inevitably increases in the face of an obviously growing need to curtail costs.

There are those who say that the supply of resources would be adequate to meet the demand for services if ineffective and unnecessary services were eliminated, and they call upon the medical profession to help bring this about. At best, however, and even if fully accomplished, this would do only for a while because the disparity between a virtually unlimited demand for services and clearly limited resources can only increase. In the meantime, many who are powerfully situated believe that the cost control measures that are being imposed, including putting physicians in the position of "gatekeeper," with responsibility to protect quality while controlling costs in patient care, will force physicians and the medical profession to do what no one really wants to do: be responsible for rationing care. Harry Schwartz put his finger right on it. Physicians are being placed in the role of "double agents" in health care. On the one hand, they want and are expected to be advocates for patients' interests, while on the other, they are finding themselves to be increasingly locked into being unhappy front-line agents for those whose goals are to achieve cost control.

It surely would not sit well with patients or the public if it became generally known that physicians were being maneuvered into becoming *de facto* double agents in patient care—and this very much against their will, their tradition, and their ethics, which have always put patients' interests first. As Schwartz suggests, perhaps it is time for physicians and organized medicine to begin to publicize to their patients and the public the fact that society itself is forcing physicians to become what amounts to double agents in patient care, and that this is not in the long-term interests of either patients or of society. If there is to be integrity and trust between doctor and patient, and this has always been a *sine qua non* in patient care, then a physician's first duty must be to a patient. Patients expect nothing less, and in the final analysis, society expects nothing less.

It would not only be a tragedy but a disaster for medicine if physicians and the medical profession were, by their own default, to become institutionalized as "double agents" in this nation's health care system. What is urgently needed now is for society, whether in the form of government, health insurance programs, or health care plans, to decide and make clear what they will pay for in health care and what they will not. This would free physicians to do what they should do and are trained to do—what they think is best for their patients—and do this within the framework of whatever resources society decides it can afford. This will not be easy to do, but the stakes for patients and the public are very high indeed.

There may, however, be a precedent worth some thought and study. As Dr Kitzhaber points out elsewhere in this issue, the state of Oregon has been one of the first to recognize and face this problem and has already begun to take some steps to deal with it. But there is as yet no widespread general awareness. The immediate need is for affirmative action by individual physicians with their patients and by the medical profession with society as a whole to publicize this issue and then to work with the payers of health care to find ways to separate the roles of church and state, so to speak, or in health care, the appropriate roles of physicians and society.

MSMW

What Do Stroke and Brain Trauma Have in Common?

While many investigations of acute central nervous system (CNS) injury are now emphasizing cellular mechanisms, improved patient care is still the ultimate goal of this research. An important underlying hypothesis is that populations of dysfunctioning neurons intermix with or surround areas of dead or dying neurons and that these cells, while vulnerable, may recover if the local environment can be altered from unfavorable to favorable. Studies of later recovery are moving in parallel where many investigators are also studying cellular events. Particularly interesting are those that reexamine the roles of regeneration and sprouting. These issues, specifically neuronal vulnerability after injury due to unfavorable environments, drugs that may alter these environments, and the role of axonal sprouting, are addressed in this issue of the Journal by Becker and associates, "Brain Cellular Injury and Recovery—Horizons for Improving Medical Therapy in Stroke and Trauma."

The reader whose experience is outside the area of CNS injury may ask, why stroke and trauma? Although they account for the major proportion of CNS-related death and disability, the two conditions are distinctly different. While differences are obvious, however, there are at least two important reasons to consider and, further, to study them together. First, there are abundant data showing a coexistence of traumatic brain injury and events that can cause cerebral ischemia and hypoxia in a high proportion of head injury

cases. Second, important cellular events that cause secondary injury may be similar or even identical in both stroke and trauma. The animal models described by the authors, employing sequential injury—impact followed by ischemia—are, then, appropriate from both perspectives. Further, these models at least indirectly address the central hypothesis of increased neuronal vulnerability and secondary cell death after injury. They also define specific candidate mechanisms that may underlie this vulnerability and provide new directions for therapy.

Several published reports have demonstrated the coincidence of head injury and shock or hypoxia. For example, consider data from the pilot phase of the national Traumatic Coma Data Bank.[1] In that study, data were collected prospectively on almost 600 patients. Of these patients, 20% were considered hypoxic before admission, as defined by an initial partial arterial oxygen pressure of 60 torr or less, or by a history of apnea in those patients ventilated before their arterial blood gases were measured. Shock occurred in 33% of the population as defined by a systolic blood pressure of 90 torr or less before admission. Shock was associated with a 30% increase in the frequency of the outcome of brain death or vegetative state, while hypoxia was associated with about a 20% increase in this outcome. Additionally, in association with these insults there were relatively fewer patients who were considered to have a good outcome or to be only moderately disabled. These associations were statistically significant. Further, while there is, no doubt, an association between multisystem injury and either shock or hypoxia, a statistically significant association between multisystem trauma and outcome could not be found in this population. Data from the full-phase study, which includes information from more than 1,000 other patients, are currently undergoing analysis and also show the importance of early hypoxia and shock in patients with severe head injury.

What are the specific cellular mechanisms common to stroke and trauma that could cause increased neuronal vulnerability in secondary cell death? Those currently under the most intensive investigation and discussed by Becker and co-workers have a central theme of the release of substances from injured or dying cells, substances assumed toxic to nearby neurons spared by the initial precipitating event. These mechanisms include the accumulation of lactate and acidification of the local environment; cell-membrane breakdown, lipid peroxidation, and release of free radicals; and excessive release and accumulation of neurotoxins and excitatory synaptic transmitters, particularly glutamate. A recently published report from the Cornell group headed by Plum and Pulsinelli has provided important direct evidence that lactate in concentrations like those found after ischemia can cause neuronal death.[2] These investigators studied the histologic appearance of rat brains that had been subjected to microinjections of various concentrations of lactate. The idea that lactate or hydrogen ion is toxic to neurons now seems secure. In view of the controversies surrounding this idea, it is surprising that this experiment was not done earlier. Also recently reported and interesting are the findings of Pitts and associates.[3] They studied a sequential injury model using magnetic resonance spectroscopy. Pertinent to the hypothesis under consideration here was the finding that intracellular pH and high-energy phosphate concentrations (adenosine triphosphate and creatine phosphate) decreased when both injuries were combined—impact followed by hypoxia—to a much greater degree than when the two injuries were studied separately.

While the idea that glutamate in high concentrations may act as a neurotoxin is not new, compounds that would easily penetrate the blood-brain barrier and act as specific receptor (*N*-methyl-D-aspartate) antagonists have only recently become available, and one such compound, MK-801, has been shown in animal models of ischemia to have beneficial effects.[4] Of the three outlined mechanisms, the release of free radicals as a cause of secondary neuronal injury in animal models has been the most widely supported; data have been generated from many laboratories under a wide variety of conditions. The evidence is sufficiently impressive to warrant a clinical trial in the context of a multicenter study, and the United States Department of Defense has funded such a trial of superoxide dismutase in patients with missile injuries of the brain.

There has been considerable progress in studying these mechanisms, though their clinical importance must await further study. It is hoped that when indicated, they will be tested by multicenter, randomized trials. The clinical importance of cellular mechanisms in the animal studies of long-term recovery, particularly those indicating a possible role for axonal sprouting, will obviously be more difficult to evaluate. These findings are potentially the most exciting, however, and these kinds of experiments should be encouraged.

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Uncompensated Care

"MY JOB AS A PHYSICIAN is to serve as an agent of trust and to do anything appropriate to provide necessary medical care and not to serve as a rationeer of scarce resources on an individual basis." This statement of Dr Nancy Dickey, chair of the American Medical Association's Council on Ethical and Judicial Affairs, expressed the convictions of most physicians. None of us, as physicians and human beings, want to make our professional decisions for our patients primarily for fiscal reasons. We desire to give them quality care and to be their advocates when needed.

Society may change this. It may mandate us to render inadequate or improper services if the problems associated with uncompensated care are not solved. The growing crisis of caring for those who are uninsured, underinsured, and uninsurable, according to Dr John Kitzhaber, ". . . poses one of the most serious threats facing the medical profession today." It can result in a deterioration of health for a growing number of Americans, with very serious social and economic consequences.

Dr Kitzhaber, whose address to the California Medical Association House of Delegates at its 1988 annual meeting is

published elsewhere in this issue, is a practicing physician in Roseburg, Oregon, and a state legislator. At age 41, he is president of the Oregon State Senate and an expert dealing with a variety of issues including public education, land use planning, water policy, and health care. His discussion of the problem of uncompensated care—its etiology, its symptomatology, its prognosis, and its possible cure—reveals the depth of his concern and expertise.

The problem of uncompensated care—giving services to those with no means to pay—is not new in America. It has been present since colonial days, and yet, the poor have always received a modicum of health care. Some came from charity but most, because of the influence of the Elizabethan poor laws, came from local political subdivisions: towns, cities, or counties. Both the facilities and the care were primitive, barely giving enough sustenance to sustain life. Gradually, the poor farms and pesthouses of the past century gave way to county hospitals, some of which became the great teaching institutions of today affiliated with medical schools. Before the 1960s the poor had easy access to these institutions. Although the accommodations on bleak and crowded wards were usually spartan, the quality of both medical and nursing care often equalled or exceeded that given in private institutions. Most of the nonprofit and religion-controlled hospitals gave a substantial number of people care at reduced rates. The fee-for-service system in existence then allowed and even encouraged providers—both physicians and hospitals—to shift costs. It permitted them to charge the wealthy more in order to pay for the care of the poor.

The principle of universal access mentioned by Dr Kitzhaber, "the idea that all Americans, regardless of their income, should have access to the health care system and to all the services it had to offer," came into full fruition during the 1960s with the enactment of Medicare and Medicaid and the growth of "private health insurance policies funded primarily through employment."

For a while this system worked quite well. America seemed to have achieved "an ideal health system." Almost everyone had access to mainline quality care: the elderly were covered by Medicare, the workers and their families by employer-funded insurance, and the poor by Medicaid. This egalitarianism of care prompted third-party payers to pay a consistent and uniform fee to each provider. This seemed fair, but over the years it effectively stopped cost shifting.

Meanwhile, the overall cost of health care escalated in two decades from 7% of the gross national product to the current 11%. This resulted from many factors, including a growing population, especially of older people, increased technology, inflation, rising expectations, and growing demands for more services. As the costs of care increased, the prosperity of the country declined, the national debt increased, workers' productivity decreased, and American businesses could no longer compete with foreign manufacturers, either abroad or at home. Neither the public nor the private sector could afford the high cost of medical care. Both reacted by cutting back their coverage. This widened the gap between the two, leaving more people without health insurance. Since these people have limited fiscal resources, they can either go without medical services or seek uncompensated care. Since shifting of costs is no longer allowed, providers are reluctant to care for this growing segment of the population.

To date, little has been done to resolve the problem except to lay blame on providers. Since physicians are perceived to be wealthy, many members of society feel that doctors should be mandated to take charity cases. In fact, some legislatures are considering making this a requirement for continued licensure. Because many nonprofit hospitals received federal funds in the past, they had an obligation to care for uncompensated patients. More and more nonprofit hospitals, however, are closing their doors because of financial difficulties. This compounds the problem. The absence of cost shifting makes the providers—physicians and hospitals—face the prospect of caring for more patients without adequate recompense, refusing them care, or sending them elsewhere: "dumping."

Neither of these alternatives leads to meaningful care for these unfortunate people. Dr Kitzhaber believes society must make the hard decisions needed to solve the problem of uncompensated care by creating a new system of health care based on limited resources and acceptance of the fact that the well-off can purchase more health care than the poor—the reality of implicit rationing. "The government," he states, "should pay for the poor regardless of their age" but not for the elderly. The new health care system that Dr Kitzhaber recommends would have a minimum of three tiers: government-sponsored for the poor; employer-funded for the workers; and a traditional fee-for-service tier for those who wish to buy the type of health care they desire.

As this concept develops, the medical profession has the responsibility of defining the various levels of care, especially the basic and minimal level available to the poor. This means that the emphasis must be placed on what is best for society, not what is best for the individual. Once the basic level of health care is defined, society has no recourse except to pay for it through government funding. If society in its collective wisdom feels that additional services are needed for the poor, it has the option to provide them based upon the amount of money it wants to spend.

In a system such as this, the money spent on health care for the poor will be used most effectively for the good of society. Working with these patients, physicians know the limitations of their service; they are not being put in the role of rationeer. If, according to Dr Kitzhaber, they feel their patients need more than the government allows, they can truly be advocates by appealing on their patients' behalf. This would allow physicians to continue to serve as agents of trust and to do anything appropriate to provide necessary medical care.

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Suction-Assisted Lipectomy—Caveat Emptor

THE ARTICLE BY BELLO and co-workers elsewhere in this issue adds to our knowledge and awareness that severe infections may ensue following suction-assisted lipectomy. The medical profession was warned of this possibility in 1982 by the ad hoc committee that was formed by the American Society of Plastic and Reconstructive Surgeons to study the subject. Five years later and with an experience of more than 100,000 cases, the society reported to the profession and the public at large a total of 11 deaths and 9 cases of serious life-threatening complications.[1] Several of the deaths were attributed to severe necrotizing fasciitis.

As with any operation, the prospect of serious infection with suction-assisted lipectomy is ever present. The risk clearly increases if the wounds are near the perineal region, and sterility is compromised by the manual manipulation that is required of the procedure. If contamination inadvertently occurs, the repetitive penetration of the soiled cannula into the depths of the areas treated can result in a disastrous widespread infection in a closed space. This occurred in a case where a physician chose to do liposuction following a tubal ligation. Having accidentally perforated the bowel with the suction cannula, fecal contamination was repeatedly plunged into multiple operative sites. A catastrophic life-threatening gram-negative infection of the abdomen, flanks, and thighs resulted.

Liposuction has wide public appeal and has rapidly become the most common cosmetic operation in the United States. This lure has elicited many ill-trained practitioners with limited surgical training or experience. Furthermore, in an attempt to court patients by lowering costs, many of these procedures are being carried out in substandard office environments that are staffed by ill-schooled personnel and where the usual operating room infection control practices are nonexistent.

Although some may elect to use prophylactic antibiotics, this use is not an umbrella against a sloppy technique. That devitalized fat is left behind is undoubtedly true; a convenient pabulum for bacteria is thus established. Equally important is the appreciation of large fluid shifts, hypovolemia, and anemia that occur if more than 2,000 ml of aspirant is removed and autologous replacement is not provided. The resulting circulatory embarrassment leaves the patient with a crippled defense. In addition, the peril of pulmonary embolism of fat or blood is always present.

Liposuction is not an innocuous procedure that can be held in casual regard. As with any other operation, it should be done in an appropriately controlled environment where peer review and accreditation of the facility exist. It can be carried out safely in well-equipped outpatient office facilities where scrupulous operating room sterility is the standard and proper patient selection is practiced. Without contest, all would agree that the procedure should only be done by practitioners with the proper background and experience in general surgery.

The ad hoc committee of the American Society of Plastic and Reconstructive Surgeons concluded that "in the hands of properly trained surgeons, suction-assisted lipectomy is normally a safe and effective means of surgically contouring localized fat deposits that do not respond to diet and exercise." Those who lack the essential training and discipline and, yet, insist on practicing liposuction are a constant threat and an imminent danger to the public at large. If we cannot professionally set proper criteria of safety in the interest of the public, governmental intrusion will surely occur and, perhaps, that time has come.

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Case Reports

Mesenteric Panniculitis

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MESENTERIC PANNICULITIS is a nonspecific inflammatory process involving adipose tissue of the mesentery. It occurs rarely and is virtually unknown to many pathologists and surgeons. Experience with this case prompted reporting of this challenging study.

Report of a Case

The patient, an 80-year-old man, was admitted to El Dorado Hospital and Medical Center (Tucson) to undergo a cholecystectomy for cholelithiasis. A physical examination showed no abnormalities. The abdomen was soft, with no palpable masses or tenderness. There were no abnormal laboratory findings, except for a leukocyte count of 12,000 per μl. During an otherwise uneventful cholecystectomy, multiple masses of various sizes that appeared yellowish gray, flat, smooth or lobulated, and fairly well defined were found in the mesentery of the small intestine. These were separated by grossly normal mesentery. A wedge biopsy specimen of one of these masses showed sheets of foamy macrophages replacing adipose tissue of the mesentery and branching fibrous bands infiltrated by a small to moderate number of lymphocytes. A few lymphoid nodules and scattered neutrophils and eosinophils were also present. These findings were consistent with the diagnosis of mesenteric panniculitis (Figures 1 and 2). The gallbladder showed chronic inflammation and contained multiple calculi. The postoperative course was uneventful, and the patient was discharged six days after the operation.

Discussion

Mesenteric panniculitis was first described by Jura in 1924, who also coined the term "retractile mesenteritis."[1] Other terms used for this disorder included isolated lipodystrophy, a form of mesenteric tumor described by Crane and co-workers[2]; mesenteric panniculitis reported by Ogden and associates[3]; mesenteric manifestations of Weber-Christian disease noted by Herrington and colleagues[4]; mesenteric lipogranuloma described by Weeks and co-workers[5]; liposclerotic mesenteritis studied by DeCastro and associates[6]; and mesenteric lipodystrophy reported by Kipfer and colleagues.[7]

In 1977 Durst and co-workers reviewed 68 cases reported by 23 authors and noted the benign nature of the disease.[8] The 53 cases studied by Kipfer and associates at the Mayo Clinic were added,[7] with an overall age range of 20 to 80 years, a mean age of 60, and 64% of patients being male. In this study, 43% of patients were asymptomatic, and panniculitis was found incidentally during an intra-abdominal operation most commonly done for gallbladder disease. In the remaining patients, the most common presenting symptom was abdominal discomfort—ranging from vague fullness and heaviness to pain—most often felt in the upper abdomen. Less frequent presenting symptoms included nausea, obstipation, diarrhea due to partial obstruction of the small bowel,[9] anorexia, weight loss, back pain, pyrosis, and, rarely, an acute abdomen.[10] The original symptoms varied in time of initial onset from 2 weeks to 16 years, with a mean duration of 6 months. About 72% of patients had had symptoms for less than a year.

The most common physical finding was a poorly defined, deep-seated mass or masses in the left upper quadrant. These were firm to hard, fixed or movable, and they frequently transmitted the aortic pulsation. This explains why some cases have been falsely diagnosed as abdominal aortic aneurysm.

Laboratory findings were generally within normal limits or nonspecific. A mildly elevated sedimentation rate was found in 60% of patients. The results of gastrointestinal barium studies were usually normal. In some patients dis-

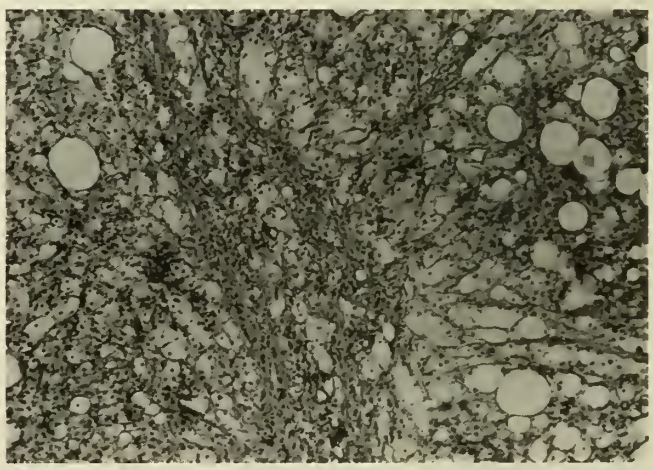

Figure 1.—Sheets of foamy macrophages replace adipose tissue of mesentery. Fibrosis is also present (hematoxylin and eosin, original magnification × 10).

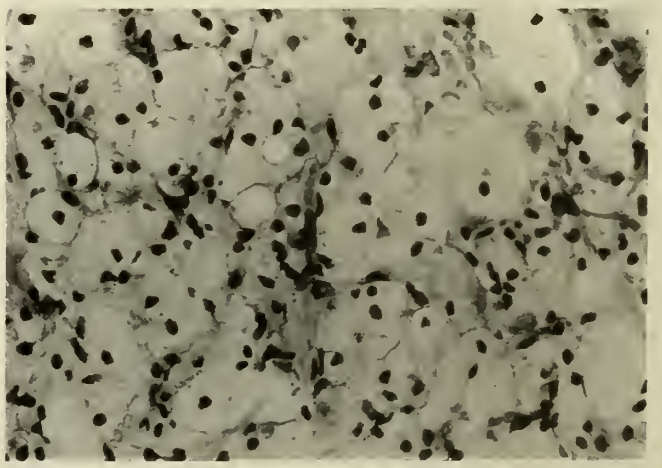

Figure 2.—A higher power view of the same tissue as in Figure 1 shows sheets of foamy macrophages (hematoxylin and eosin, original magnification × 40).

(Khachaturian T, Hughes J: Mesenteric panniculitis. West J Med 1988 Jun; 148:700-701)

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placement of the intestinal loops by an extrinsic mass or dilated loops of small intestine was noted.

During the surgical procedure, three patterns of mesenteric involvement were noted: diffuse mesenteric thickening (43%); a single, discrete, smooth or nodular tumor (32%), usually involving the jejunal mesentery; and multiple discrete tumors of 1 to 10 cm, usually involving the mesentery of the jejunum and terminal ileum. These different types of mesenteric panniculitis can be mistaken grossly for various inflammatory and neoplastic conditions.

Microscopic examination of surgically removed masses or biopsy material showed sheets of foamy macrophages replacing the fat. Scattered lymphocytic nodules without germinal centers and mild lymphocytic infiltration were seen in some cases. Acute inflammatory cell infiltrate was minimal or absent. Fibrosis, usually of a mild to moderate degree, was present in 25% of cases. Necrosis, cholesterol clefts, occasional multinucleated giant cells, and calcification were noted in some cases. The most frequently associated diseases were cholelithiasis and coronary artery disease. Less commonly, benign or malignant diseases, such as diabetes mellitus, aortic aneurysm, colorectal polyps, diaphragmatic hernias, adenocarcinoma (duodenum, ovary, pancreas, or rectum), squamous cell carcinoma of the esophagus, and seminoma were associated with this disorder. These associations were within the range of the expected incidence for this age group.

Recent observations regarding the diagnosis of mesenteric panniculitis may be helpful to clinicians and may provide a stimulus for further investigation. Kuhrmeier has suggested that this disease is more common than is reported, based on his findings in 9 of 712 autopsies (1%).[11] Cakmak and co-workers, reporting the disease in a 4-year-old boy, also speculate that the incidence in children may be greater than previously reported.[12] Katz and associates have contributed observations on findings with computed tomography.[13] Janisch and colleagues suggest that the combinations of ultrasonography and guided tumor puncture may help to establish a diagnosis without laparotomy.[14]

The relationship to other diseases is also of interest. Scherrer and co-workers report a case in which mesenteric inflammation was found.[15] Later, duodenal biopsy was thought to confirm Whipple's disease and invalidate the earlier suggestion of mesenteric panniculitis. Scully, Mark, and McNeely discuss in detail the case of a 10-year-old girl seen at the Massachusetts General Hospital (Boston) with retractile mesenteritis, who had frequent febrile illness associated with abdominal pain.[16] No associated disease or diseases were found. She was maintained on a regimen of steroids, and there were no further recurrences. Dor and associates describe the case of another 10-year-old girl with intra-abdominal panniculitis preceding systemic lupus erythematosus.[17] A single case of mesenteric lipodystrophy, reported by Dinesoy and co-workers, was associated with cholesterol ester storage disease.[18] In studies done by Cherayil and colleagues, significant amounts of cholesterol esters were found in mesenteric fat from six patients with mesenteric panniculitis.[19]

Recent thinking on therapy for mesenteric panniculitis suggests that, when not associated with other diseases, this condition is self-limiting. In a case of mesenteric panniculitis described by Schwab and Hofstädter as Pfeifer-Weber-Christian disease of mesentery,[20] antirheumatic therapy resulted in an excellent response. In two patients with an aggressive form of sclerosing mesenteritis, Bush and co-workers reported a dramatic response to the administration of cyclophosphamide.[21] They recommend such early aggressive chemotherapy when tubulorectal structures are present within the biopsy specimen, suggesting an autoimmune origin of sclerosing mesenteritis.

The etiology and pathogenesis of this process are obscure. Blunt or surgical trauma, thermal or chemical injury, vasculitis, avitaminosis, autoimmune disease, leakage of bile and urine, and hypersensitivity reactions have been suggested as possible causes. An abnormal lipid composition of fat tissue in mesenteric panniculitis has been documented.[19]

In summary, mesenteric panniculitis is a nonspecific, predominantly benign inflammatory process involving the mesentery of the small intestine. On gross examination, the disease may be mistaken for several benign or malignant—inflammatory and neoplastic—processes, including liposarcoma. On microscopic examination, sheets of foamy macrophages may be mistaken for lipoblasts, resulting in an erroneous diagnosis of liposarcoma. When the disease is found during an operation, a frozen section study is warranted. The presence of sheets of benign foamy macrophages replacing adipose tissue of mesentery should suggest the diagnosis of mesenteric panniculitis. Because the natural history of this disease is usually benign, a radical resection is unjustified. The pathogenesis of this disorder deserves further research.

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Kaposi's Sarcoma in a Patient With Rheumatoid Arthritis and Polymyositis Treated With Corticosteroids

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KAPOSI'S SARCOMA is more prevalent in immunocompromised patients. It has been documented in patients with lymphoid malignant disorders,[1] renal allografts,[2,3] and more recently in patients with the acquired immunodeficiency syndrome (AIDS).[4] Evidence is mounting that Kaposi's sarcoma occurs with greater frequency in patients with autoimmune diseases. With the exception of the AIDS-associated cases, a common thread among the other high-risk groups is the concomitant use of corticosteroids with or without other immunosuppressive agents. We herein present the case of a man in whom Kaposi's sarcoma occurred in conjunction with rheumatoid arthritis and polymyositis, and we review the literature available on the association of Kaposi's sarcoma with autoimmune disorders and corticosteroid therapy.

Report of a Case

A 57-year-old man was admitted to UCLA Medical Center in 1965 for the diagnosis and treatment of Kaposi's sarcoma. Four years before admission the patient was diagnosed to have seropositive, nodular, erosive rheumatoid arthritis and Raynaud's phenomenon. He was given salicylates and low doses of prednisone. Three years later the patient had pronounced symmetric proximal muscle weakness, an elevated serum creatine kinase level to 2,003 units per liter (normal range 21 to 215), an abnormal electromyogram, and a muscle biopsy confirming a diagnosis of polymyositis. The biopsy specimen showed no evidence of steroid-induced myopathy. A good clinical response was obtained to treatment with 60 mg of prednisone a day. The creatine kinase level decreased to the normal range, and the proximal muscle strength increased. Two months before admission, multiple violaceous skin nodules developed on both lower extremities. The patient had no preexisting nodular skin lesions before treatment with high-dose corticosteroids.

On examination the vital signs and the head, eyes, ears, nose, and throat were normal. Lymphadenopathy was noted in the anterior cervical lymph node chain. Rales were heard in the posterior lower lobes of the lung. Examination of the heart revealed a murmur of aortic sclerosis confirmed by echocardiography, the liver was palpated 5 cm below the right costal margin, and the findings of the abdominal examination were otherwise normal. Dependent edema was noted in the lower extremities, along with multiple small—2 to 6 mm—round, discrete, violaceous nodules on the skin (Figure 1).

The musculoskeletal examination revealed symmetric synovitis in the proximal interphalangeal joints, metacarpal phalangeal joints, elbows, and knees. Both olecranon and prepatellar bursae were enlarged. A 0.5-cm nodule was discovered in proximity to the left elbow. Muscle testing showed 4/5 strength in all proximal muscles.

Laboratory studies elicited the following values: hemoglobin, 10.5 grams per dl; leukocyte count, 7,400 per μl with a normal differential; erythrocyte sedimentation rate, 53 mm per hour (Wintrobe); and elevated levels of serum aspartate aminotransferase (glutamic-oxaloacetic transaminase), lactic dehydrogenase, and creatine kinase. A urinalysis disclosed trace amounts of protein, but was otherwise normal. The rheumatoid factor was 1:160, tests for the antinuclear antibody and lupus erythematosus preparation were negative, and the third and fourth component of complement and total hemolytic complement values were also normal. The diagnosis of Kaposi's sarcoma was confirmed by a skin biopsy, with the presence of rheumatoid arthritis confirmed both by biopsy of the nodule and typical clinical and radiologic findings. The diagnosis of polymyositis was reconfirmed by the clinical presentation, elevated muscle enzyme values, classic electromyographic findings, and deltoid muscle biopsy findings. Bibasilar interstitial infiltrates were present on chest radiographs. Liver enlargement was thought to be due to passive congestion and lymphadenopathy related to rheumatoid arthritis with local joint involvement.

Radiation treatment of the skin lesions was considered, but before treatment could be initiated, the patient was discharged to his primary physician and died six months later of heart failure complicated by pulmonary insufficiency.

Discussion

Kaposi's sarcoma was first termed "multiple idiopathic pigmented hemangioma" by Moritz Kaposi in 1872.[5] The classic presentation of Kaposi's sarcoma is that of one or more skin lesions occurring predominantly on the extremities in elderly men of Jewish or Italian lineage.[6] It is now recognized to have an increased prevalence in immunocompromised hosts. With regard to autoimmune diseases, Kaposi's sarcoma has been reported in patients with rheumatoid arthritis,[7-9] systemic lupus erythematosus,[10,11] dermatomyositis,[12] polymyositis,[13,14] polymyalgia rheumatica,[8] and temporal arteritis.[15] All of these cases occurred in patients receiving corticosteroids systematically. In a recent case report, Kaposi's sarcoma developed in a homosexual man with Henoch-Schönlein purpura after six months on oral prednisone therapy.[16] Our patient is unique for having two connective tissue disorders with the subsequent development of Kaposi's sarcoma during corticosteroid therapy. The presence of rheumatoid arthritis and polymyositis in this patient was well documented by clinical, serologic, radiographic, and histopathologic findings.

Review of these cases has not shown a clear time- or dose-dependent relationship between corticosteroid treatment and the onset of Kaposi's sarcoma lesions, although the duration of steroid therapy in most cases was at least four months. Spontaneous tumor regression has been reported with complete clinical remission in certain patients after discontinuing the corticosteroid therapy or other immunosuppressive agents.[12,15,16]

(Weiner SR, Noritake DT, Paulus HE: Kaposi's sarcoma in a patient with rheumatoid arthritis and polymyositis treated with corticosteroids. West J Med 1988 Jun; 148:702-703)

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The mechanism by which Kaposi's sarcoma arises in patients receiving corticosteroids is not well understood. Postulated mechanisms have included the activation of latent oncoviruses as a result of chronic immunosuppression, in addition to the presence of aberrant immune responses related to the underlying disease.[2,8,10] Genetic influences may also play a role in the development of this particular neoplasm in immunocompromised persons.

Our patient had Kaposi's skin lesions in a distribution more typically seen in the "classic" form of the disease—that is, confined to the skin and localized to the extremities. The variety of Kaposi's sarcoma seen in association with AIDS more commonly presents with lesions on the torso as well and can occur in disseminated forms with significant visceral involvement. Visceral involvement occurs in as many as 10% of cases of the classic variety, and, to date, only one case of disseminated Kaposi's has been associated with corticosteroid therapy in a patient with systemic lupus erythematosus.[11] Unfortunately, it is not known whether our patient had pulmonary involvement with Kaposi's sarcoma or whether the interstitial lung disease was a direct manifestation of either his rheumatoid arthritis or polymyositis. We cannot comment on the serologic status of this patient with regard to antibodies to the human immunodeficiency virus, as the case occurred before the initial descriptions of AIDS. All of the clinical features, however, are consistent with manifestations of rheumatoid disease or polymyositis.

This case highlights the need for physicians to be aware that drug-induced immunosuppression with corticosteroids presents a significant risk factor to the development of Kaposi's sarcoma and that withdrawing the immunosuppressive therapy can result in a complete clinical remission. The skin lesions of Kaposi's sarcoma can easily be mistaken for cutaneous vasculitis, particularly in patients with autoimmune diseases on corticosteroid therapy. It is therefore important to recognize the increased risk of Kaposi's sarcoma in such patients and to differentiate this early on from vasculitis so that therapeutic agents can be instituted or immunosuppressive therapy discontinued.

Figure 1.—The photograph shows discrete nodular lesions over the lower extremities.

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Fasciitis and Abscesses Complicating Liposuction

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SUCTION LIPECTOMY was first done in this country in 1976.[1] In the past few years the procedure has been widely publicized by the media, and the number of surgeons doing liposuction has risen dramatically.[2]

If patients are carefully selected, with good skin tone, localized fat deposits, and normal weight, the cosmetic results are reportedly excellent.[1-3] Possibly because this procedure has only recently been introduced, there has been a paucity of studies that critically examine the complication rates in large numbers of cases. The few studies available

(Bello EF, Posalski I, Pitchon H, et al: Fasciitis and abscesses complicating liposuction. West J Med 1988 Jun; 148:703-706)

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Figure 1.—The photograph shows a patient with ecchymoses of both medial thighs seven days after a lipectomy procedure.

Figure 2.—The lateral right thigh of the same patient shows substantial erythema and edema (day 7 after a lipectomy).

suggest that the incidence of infectious complications is low.[1,2] The following is a report of a case of a patient in whom a severe soft tissue infection developed complicating liposuction.

Report of a Case

The patient, a 43-year-old woman, had undergone a facelift procedure and suction lipectomy of the abdomen and thighs as an outpatient a week before she was admitted for high fevers, mental state changes, and infections at several soft tissue surgical sites. The patient had a history of earlier cosmetic surgical procedures without complications, including bilateral breast augmentation and bilateral blepharoplasty. Five days before admission, she had fever and rigors and excruciating pain had developed at both thigh liposuction sites.

On physical examination at the time of admission, she was lethargic and appeared younger than her stated age. Her vital signs included a temperature of 39.8°C (103.6°F), pulse rate 144 beats per minute, and blood pressure 92/66 mm of mercury. There were bilateral 1.5-cm long incisions at the buttock-thigh border. The proximal third of the left thigh showed moderate ecchymoses medially and posterolaterally with mild overlying erythema and induration (Figure 1). The right thigh was exquisitely tender and ecchymotic with notable soft tissue erythema and edema extending posterolaterally from the level of the femoral triangle in the groin to two thirds the distance to the popliteal fossa (Figure 2). There was no localized fluctuance or crepitance of either leg. In the suprapubic area, the 1-cm long incision exuded a small amount of sanguinopurulent material and was surrounded by a mild amount of erythema and tenderness. She had a summation gallop but no heart murmurs. The findings of the pelvic and rectal examinations were within normal limits as

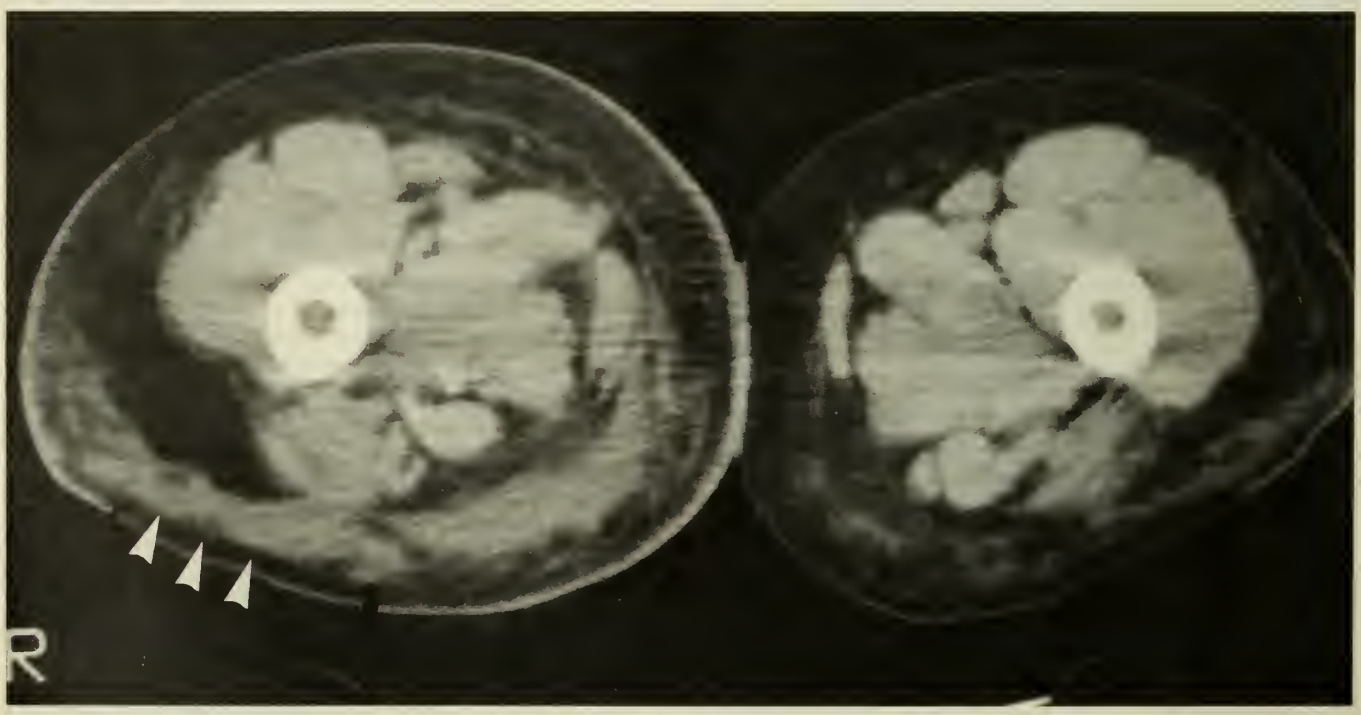

Figure 3.—A cross-section computed tomographic scan of the lower extremities at the level of the upper thigh shows pronounced soft tissue swelling, extensive separation of fascial planes, and abscess formation (**arrows**).

was the rest of her abdomen except for the skin changes described. She was lethargic but easily arousable and was oriented without focal neurologic deficits.

Admission laboratory data showed a leukocyte count of 8,400 per μl with a normal differential, a hemoglobin of 9.6 grams per dl, and a hematocrit of 28%. No organisms were seen on the Gram's stain of the abdominal wound exudate. Routine x-ray films of the right thigh showed soft tissue swelling but no free air or bone abnormalities. After blood and wound specimens were obtained for culture, a regimen of nafcillin sodium, 2 grams every four hours; penicillin G, 3 million units every four hours; and gentamicin sulfate, 85 mg every eight hours, was begun intravenously. Warm compresses were applied to the sites of inflammation.

The next day the patient was noted to be icteric with a total bilirubin level of 3.9 mg per dl and a direct fraction of 2.8 mg per dl. Liver function tests gave the following values: aspartate aminotransferase, 158 units per liter (normal < 35); alanine aminotransferase, 63 units per liter (normal < 45); alkaline phosphatase, 144 units per liter (normal < 108); γ-glutamyl transferase, 76 units per liter (normal < 41); and lactic dehydrogenase, 602 units per liter (normal < 225). The reticulocyte count was 0.6%. Her therapy was switched to cefazolin sodium monotherapy, 2 grams every eight hours, after blood cultures were without growth at 48 hours.

The patient's temperature continued to spike to 39°C (102.5°F), and her leukocyte count rose to 23,000 per μl with a leftward shift on the third hospital day. Her abdominal wound drainage quickly resolved, but her right thigh remained extremely swollen. A computed tomographic (CT) scan done on the sixth hospital day showed an intense soft tissue inflammation and a fluid collection in the posterior aspect (Figures 3 and 4). She was taken to the operating room where an extensive right thigh fasciitis with multiple loculated abscesses was incised and drained. Culture of a specimen from one of these abscesses grew *Klebsiella pneumoniae* and *Escherichia coli,* both of which were sensitive to cefazolin and gentamicin.

Following the operation, the patient rapidly became afebrile and her bilirubin level and liver function test results returned to normal. She continued, however, to have persistent nontender induration of the right posterolateral thigh. This was thought to possibly represent fat necrosis from the combined effects of the liposuction and infection. She was discharged on a regimen of cephalexin, 500 mg taken by mouth every six hours, with some residual induration and mild erythema of the right thigh. Three months after discharge, the patient was doing well but continued to have induration without erythema, warmth, or tenderness at the site of the previous right thigh infection.

Discussion

Suction lipectomy has several attractive features. The technique is straightforward and versatile. A blunt or sharp-edged cannula is attached via a tube to a vacuum device. The cannula is introduced through a small incision into any of several localized fat deposits including the submental area, neck ("buffalo hump"), upper arms, preaxillary region, abdomen, waist, hips, buttocks, thighs, knees, and ankles.[3] Under suction, the cannula is manipulated with the intention of removing a uniform deep layer of fat. A variation on the basic technique, advocated by Illouz, is to create several regular tunnels, rather than a single cavity, to recontour the site.[4]

The infectious complications of liposuction previously reported have been rare and mild. Courtiss retrospectively described the first 100 of his patients to undergo liposuction of the thighs, knees, abdomen, flanks, and arms; infection developed in only three patients.[1] One of them had redness overlying the liposuction site from which no material could be aspirated for culture. This patient was treated with oral antibiotics with good results. The other two patients had infections at the knee and thigh, respectively. In addition to antibiotics, both required formal surgical drainage through the original incision.

In a later report, Courtiss described the cases of 50 additional patients on whom liposuction was done. The author continued to note that infection was uncommon but did not provide actual numbers. The reported "few" infectious

Figure 4.—A close-up computed tomographic scan view of the right leg at the same level as in Figure 3 shows intrafascial separation and abscesses, indicated by arrows.

cases that did occur initially presented with increased pain at the liposuction site, followed by tenseness and erythema of the overlying skin. These infections, usually caused by *Staphylococcus aureus,* responded well to the use of antibiotics, elevating the affected limb, and what was described as "simple drainage measures." Furthermore, Courtiss did not note any distinct soft tissue abscesses nor was there need to make any additional drainage incisions,[5] as in the currently reported case.

Using a questionnaire sent to 2,524 US and Canadian members of the American Society of Plastic and Reconstructive Surgeons, Pitman and Teimourian received 612 responses to inquiries about the various aspects of their liposuction experience.[2] The total complication rate of 1,249 procedures was 9.3%. Complications included hypesthesia, seroma, edema, pigmentation, pain, hematoma, and skin sloughing, with rates ranging between 0.2% and 2.6%. The rate of infection was 0.6%. There was no detail given on the nature or severity of these infections.

Our patient had previously unreported and serious soft tissue complications of suction lipectomy. After liposuction was done of her abdomen and thighs, cellulitis, fasciitis, and multiple abscesses developed at the surgical sites. Despite aggressive treatment with a combination of antibiotics given intravenously, she continued to spike high fevers associated with polymorphonuclear leukocytosis, hyperbilirubinemia, and elevated aminotransferase levels a few days into her hospital course, suggestive of sepsis.[6] A CT scan showed a localized fluid collection in her right thigh after which surgical drainage of several abscesses resulted in clinical improvement.

There are several interesting features of this patient's course. Her earliest symptom of increased pain at the operative site is similar to that described in Courtiss's infected patients. In striking contrast, however, to the mild, easily treated infections following liposuction described by others, this patient was extremely ill. She required intravenous antibiotics and an extensive drainage procedure with an incision well beyond the original one through which the lipectomy was done. Also, unlike the previous cases attributed to *S aureus,* this patient's infection involved two types of enteric gram-negative rods, *K pneumoniae* and *E coli.*

It is fortunate, but interesting, that infectious complications apparently do not develop in more patients after suction lipectomy. The procedure inherently involves traumatizing the subcutaneous fatty tissue that itself might predispose to infection. Large dead spaces, particularly in the buttocks and thighs, are intentionally created, with the potential for seroma and hematoma formation that could serve as a favorable nidus for infection. The use of drains and postoperative compression measures such as elastic taping or girdles should facilitate obliterating these dead spaces.[1] When carried out on the buttock and thigh areas especially, but at any site below the waist, the proximity to the fecal flora provides another source of possible pathogens in addition to skin flora. Finally, ecchymoses are often present and may obscure the erythema due to an early infection.

This is the first reported case of a severe soft tissue infection featuring fasciitis and abscess formation complicating suction lipectomy. Because the available retrospective series document low rates of mild infections, these serious complications appear to be relatively rare. They are potentially life-threatening, however, and must be included in the risk-benefit analysis of the procedure. Patients considering liposuction should be informed that serious infections, including those that may require additional incisions for therapeutic drainage, may occur after the procedure.

Patients should also be instructed to seek medical attention immediately should they have an increase in postoperative pain at the site of liposuction, as this is often the first indication of an infection. Last, when there is a severe infection after liposuction of the lower abdomen, buttocks, or thighs, the initial antibiotics should cover gram-negative enteric flora as well as skin flora.

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Correspondence

Closed Compartment Ischemia and Snakebite

To the Editor: Wingert and Chan are to be commended on a well-written paper detailing their extensive experience with rattlesnake bites in southern California.[1] It is important to emphasize that their recommendations should be applied with some caution throughout the rest of the western United States.

At least a portion of the ongoing controversy in the treatment of rattlesnake bites is due to the large variability of snakebites in different areas of the country. In essence, all rattlesnake bites do not behave the same way, depending on species and location around the country. Indeed, in the southwest area of New Mexico and Texas, the primary clinical problem, particularly with *Crotalus atrox,* the western diamondback rattler, seems to be one of extremity soft tissue necrosis and scarring. The use of the polyvalent antivenin is ineffective in the treatment of these complications, both clinically and in laboratory animal studies, with a relatively short lag time of a half hour between experimental envenomation and treatment.[2] The antivenin was also ineffective in preventing the effects of envenomation coagulopathy.[3]

These authors have conveyed an impression that a closed compartment syndrome does not take place with rattlesnake envenomations. I would take exception to that. This severe complication has been reported clinically many times in the literature, including one report of an envenomation to the thenar eminence causing a Volkmann's contracture of the deep volar compartment of the forearm, which is not anatomically contiguous. The fact that Garfin[4] could not confirm a compartment syndrome in a laboratory animal does not mean that it does not occur.

Allowing a compartment syndrome to occur without treatment renders a limb, particularly an upper extremity, in a "physiologically amputated" state that is usually dealt with by reconstructive extremity surgeons rather than pediatricians, neurologists, or emergency physicians. The patient would be better served to have a needless fasciotomy than to allow this severe complication to occur. Fortunately, the newer devices to measure compartmental pressure should allow more selective fasciotomies. Again, closed compartment ischemia with resulting ischemic contracture is a complication that should not be allowed to occur, nor should the reader be complacent in the thought that it cannot occur.

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Killing the Golden Goose

To the Editor: The commercialization of prepaid medical care: discount contracts and government-forced sacrifice of established medical ethics, including the unrestrained use of medical advertising, is beginning to have predictable, unfortunate consequences in the form of a variety of medical scams. Many of these quasi-ethical medical businesses seem to begin life in Orange County, California.

How do they work and what are they likely to do to you? Last week, I examined an apparently healthy 25-year-old woman who had no medical symptoms whatsoever. She did not even seek out a physician. Instead, the physician—or more precisely, his sales representative—came to her. She explained that she was working in her office when she received a telephone solicitation for a free medical examination provided she had medical insurance. When she protested that her policy had a $500 deductible, the solicitor magnanimously offered to accept only that portion of her deductible that she freely and willingly wished to pay. Understandably, she wished to pay none and the offer was accepted. That very week, at home, I took a call for my wife offering to sell her the very same kind of thorough physicial examination provided she had medical insurance. Without revealing that I was a physician I asked about the deductible and was similarly assured that all my wife need pay was whatever her conscience offered. "What tests would be done?" I asked. Beyond telling me that it would be a very thorough "Mayo Clinic" type exam, the salesman didn't seem to know. "How much would the exam cost without insurance?" He didn't know. "Are you calling from the clinic?" I asked. No, he was calling from the sales office. All in all it was very like the boiler room calls I used to get for aluminum siding a decade ago. I decided to decline.

The young woman patient, on the other hand, decided that the "free" offer was too good to pass up but brought the records to me for interpretation of all sorts of abnormalities that no one in the clinic seemed willing or able to explain to her. Tests done in this completely symptom-free young woman included an echocardiogram, an ultrasound study of her carotid arteries, ultrasound studies of the pancreas and gall bladder, more extensive blood chemistry studies than the average physician might order in a lifetime, indeed every kind of examination *except* those that required a physician's participation. She thought she had had a thorough physical examination but no physician ever saw her. Although she had an electrocardiogram and an echocardiogram, no one listened to her heart; though she had a spirogram, no one listened to her lungs; no one checked her breasts, and no one did a pelvic examination or a Pap smear. She got something that compares with buying an airplane ticket that includes everything but a pilot. No attempt was made to collect her deductible. Indeed, if you can bill for $2,000 for 30 minutes of work not even requiring a physician, why quibble about a deductible?

Another scenario is all too familiar. A medical company contacts a retirement home, a senior citizens' center, even a mobile home park—any concentration of older citizens—and offers a free "stroke screening." Most often, the offer is disguised as a public service. The procedure provided is a quick and often suboptimal ultrasound screening of the carotid arteries. The technique, when properly done, usually requires from 30 to 60 minutes. My patients describe dozens of people whisked through in an hour, and those results that I have been able to see are often not of diagnostic quality. But

is even this less than standard "public service" really free? Although admittedly a marvel of creative medical marketing, in those instances where bruits, transient ischemic attacks, or actual strokes bring the patient to my attention for further evaluation, I often find that to obtain the free examination the patient did sign something, and that something often turns out to be a Medicare form or a private insurance claim. From what I am able to learn from these patients, there is no serious attempt to collect the co-insurance as required by law, and since there is no explanation of benefits, the patient gratefully and innocently accepts the service as a free offering.

Another questionable game involves groups of medical vultures who do employ physicians who do physical examinations but pollute the effort by demanding scores of exotic blood tests, sophisticated scans, and myriads of radiographs costing thousand of dollars—diagnostic tests that most well-trained physicians would have great difficulty in relating either to a patient's complaint or diagnosis.

Even when the truth is pointed out, some patients reason, "Well, why not? I've paid into my insurance for years and never collected a cent." Perhaps if the medical well were bottomless, we should indeed do everything to everybody regardless of need—routine total body magnetic resonance imaging scans, routine serum folate studies, and two-dimensional echocardiograms on the population at large.

But the other side of the coin, as you know and the public is learning, is that for every patient who has a thousand dollars' worth of needless medical exploitation, another far sicker patient may be deprived of a badly needed hospital bed or a necessary physician visit because the fund of available medical dollars is limited, whether it comes from an insurance company, the federal government, or a private pocket.

The unscrupulous drain on already scarce medical resources is one of the factors that is already provoking supporters of medical rationing like Colorado's former governor to advocate eliminating hip transplants, pacemakers, kidney dialysis, and open heart surgery for "those who are destined to die." Indeed, we are all destined to die.

Legitimate, honest, caring physicians and their elected leaders must find some way to plug these scandalous leaks in the hull of our medical vessel or we will all drown—patient, doctor, the system, and all.

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EPOH-ESLAF?

To THE EDITOR: The January issue of the journal contained a vignette on "The Medical Uses of Hope."[1] The author overheard two researchers discussing chemotherapy results at an oncology meeting. The first could not understand the other's 74% response rate in lung cancer, when his own result with EPOH (Etoposide, Platinol, Oncovin, and Hydroxyurea), with the same patient selection, ingredients, and drug schedules, was only 22%. The second researcher's key was the addition of HOPE—another acronym for the same drugs. The author concluded that he, too, would give some HOPE to his patients.

Since there is minimal prolongation of life from chemotherapy of non-small cell lung cancer, and response rates reported usually vary between 10% and 30%, I wondered if something might be wrong with this story. Did the writer perceive the remarks incorrectly? Was something wrong with the second researcher's study design? Did he misperceive or incorrectly report his results? Were they a statistical blip out of a hundred studies with disappointing results? Since hydroxyurea is not an effective drug for lung cancer, was the article fiction?

I reviewed the abstracts for the past three years for the American Society of Clinical Oncology, the meeting where the conversation is reported to have occurred. I did not find a study with a 74% response rate. Nor did I find a combination with hydroxyurea.

I therefore decided to invent my own chemotherapy schedule by combining Elspar, simustine, leukovorin, amethopterin, and flurouracil (ESLAF), which I claimed had a 40% response rate in lung cancer. When combined with EPOH (EPOH-ESLAF), I claimed an 80% response rate. The only problem was that I give my patients full informed consent. I could not substantiate the claim. So, then I wondered if the editors of the journal would print this letter.

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Fluoride Contamination

To THE EDITOR: I would like to call your readers' attention to two statements that appeared in an article by Russell and colleagues in the November 1987 issue.[1]

In their discussion of fluoride as a naturally occurring contaminant in drinking water, the authors state that fluoride "has great public health benefit in preventing dental caries at dosages of 0.5 to 0.7 ppm in water." This citation is attributed to an article in *Pediatrics.*[2] In point of fact, the *Pediatrics* article makes no such statement. Rather, the article states that ideally, "The fluoride content of the local water supply in all communities should be adjusted to a level between 0.7 and 1.0 ppm." (The intent of the range is to allow for the fact that in areas with higher mean temperatures, more water is consumed so the fluoride concentration is adjusted downward.) This range is recommended by the American Academy of Pediatrics, the American Dental Association, the US Public Health Service, and the California Department of Health Services.

The authors also stated that "skeletal fluorosis has been observed when drinking water containing only 3 ppm is used (skeletal fluorosis becomes crippling when water levels reach 20 to 40 ppm)." This quote is attributed to a chapter on anions in the 5th edition of Goodman and Gilman's *The Pharmacologic Basis of Therapeutics.* Once again, there is no such statement in this chapter. In fact, the only mention of skeletal fluorosis in this chapter is reference to the fact that in its severest form it is a disabling disease and is designated as crippling fluorosis. The reference for this statement[3] was a study of endemic fluorosis in an area of India that had fluoride concentrations that ranged from less than 1 ppm to 16.2 ppm. There was no association of any individual case of skeletal fluorosis with any particular fluoride concentration. Further, the area was said to be one of extremely high temperatures, and the individuals studied were farmers who did strenuous work. The authors speculated that the water intake of these individuals averaged 5 liters daily.

In a later article, Singh and Jolly conclude that "The histopathological changes of endemic fluorosis occur only at

higher levels of intake than 1-4 ppm."[4] They further state that crippling fluorosis ". . . results from the continuous exposure of an individual to 20-80 mg of fluoride ion daily over a period of 10-20 years. Such heavy exposure is associated with a level of at least 10 ppm in the drinking water supply." These fluoride levels do not exist in the US, and there have been no reported cases of cripping fluorosis in the United States.

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* * *

Mr Russell and Drs Jackson and Spath respond

To THE EDITOR: We thank Dr Isman for his response to our article and will clarify our comments on the hazards of excess fluoride in drinking water.

First, we erred in our paraphrasing of the American Academy of Pediatrics Committee on Nutrition statement on fluoride supplementation. The committee reported: "The optimal systemic fluoride dose to prevent caries appears to be .05 to .07 mg per kg per day. The narrowness of the therapeutic range is emphasized by the fact that mild fluorosis has been seen with oral intakes greater than .1 mg per kg per day." Note that this is a dose per bodily weight, not per liter of water. Dr Isman has correctly quoted the ideal concentration in public water supplies as 0.7 to 1.0 ppm (mg/L).

Second, we evidently selected the wrong reference from a much longer staff report when we stated that skeletal fluorosis has been observed at 3 ppm in drinking water. A recent literature survey reveals that many authorities reported that skeletal fluorosis may occur at levels above 3 ppm or above 4 ppm, though bone changes can be detected at lower levels. For example, the World Health Organization (WHO) stated, "Skeletal fluorosis has been observed in persons when water contains more than 3-6 mg of fluoride per liter depending on intake from other sources."[1] It is well recognized that the total fluoride intake is affected by factors such as climatic conditions, amount of drinking water consumed, fluoride intake from sources other than drinking water, food habits, and malnutrition, which would influence the development of fluorosis.[2] A second WHO report noted that in tropical countries where dietary intake of fluoride from other sources is high, "Relatively marked osteofluorotic symptoms were connected with fluoride levels as low as 1-3 mg/litre drinking water."[2] The National Academy of Sciences stated that "Skeletal fluorosis has been observed with use of water containing more than 3 mg/liter,"[3] and the Environmental Protection Agency reported that "Bone changes (increased bone density; calcification of sacrospinous and sacrotuberous ligaments) described in this study [a study of bone density in Texas and Oklahoma] were found when the drinking water contained 4-8 mg/L."[4] A Finnish study of bones from cadavers reported histomorphometric bone changes at 1.5 ppm.[5]

WHO has stated that daily intake exceeding 8 mg (equivalent to 4 mg per liter in water at 2 liters a day consumption) is suggested to be harmful in adults. WHO recommends an upper limit of 1.5 mg per liter in drinking water. A recent study in Senegal, however, found that in a hot dry climate where water intake is high, the WHO limits did not protect adequately against crippling skeletal fluorosis or dental fluorosis, and that for such climates the limits should be set lower.[6]

Our concern with the Environmental Protection Agency's raising of the federal primary drinking water standard from a maximum of 2.4 to 4 mg per liter is that dental mottling could occur in children, especially if the secondary (voluntary) standard of 2 mg per liter is not adhered to. The National Research Council has stated that dental mottling, depending on temperature, "may occur to an objectionable degree with fluoride concentrations . . . of only 0.8-1.6 mg/liter [ppm]."[3] California has therefore retained the earlier primary limits ranging from 1.4 mg per liter in hotter climates to 2.4 mg per liter in cooler climates to try to prevent objectionable and potentially psychologically damaging mottling and pitting of the teeth of children and adolescents.

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Pediatric Liver Cancers

To THE EDITOR: The February 1988 article by Tong and Govindarajan prompted me to write.

During the years 1965 to 1970, I worked in a mission hospital in Kenya, Africa. Our 120-bed hospital treated very many cases of acute hepatitis with jaundice. Also, several times each year we admitted a small child with liver cancer. The livers were firm and multinodular. No biopsies were done.

Since it is now known that hepatitis B is common in Africa, it is possible that these malignant lesions were due to hepatitis B virus. A long-term study in Africa should add much to our knowledge of the epidemiology of these pediatric liver cancers.

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Carpal Tunnel Syndrome

To the Editor: The article on carpal tunnel syndrome by Hodgkins and Grady in the February issue[1] left several major issues unexplored. Errors in diagnosis are common. We have seen many patients who have had unnecessary treatment—for example, injection of steroids into the carpal tunnel, a procedure that may cause median nerve injury, as well as operative decompressive procedures—because of misdiagnosis. Such patients have had a variety of disorders, including proximal nerve entrapment syndromes, brachial plexus injury, idiopathic brachial plexopathy, thoracic outlet syndrome, cervical radiculopathy, and vasculitis. It is true that many patients can be conservatively treated, but the loss of function of a hand is so disabling that it is important to establish a precise diagnosis before extensive trials of therapies are initiated that may be potentially hazardous.

The authors list conditions associated with or mimicking the carpal tunnel syndrome but do not really discuss differential diagnosis. Further, in discussing the clinical findings, the sensory examination is not ever mentioned despite its importance. Electrodiagnostic studies are also very important in establishing that there is a focal entrapment neuropathy, identifying the site of the lesion, determining its severity, and excluding other disorders that may present with carpal tunnel syndrome, such as subclinical polyneuropathy. Experience has convinced me that all patients should be investigated electrophysiologically before operative intervention.

The authors indicate that the operative treatment should be by a hand surgeon. The reason for this preference is not clear because many neurosurgeons have been treating carpal tunnel syndrome extremely well for a long time.

The abstract of the paper states, "Patients for whom medical treatment fails or who present with weakness or thenar atrophy should be referred to a competent hand surgeon." It would seem equally important to stress the necessity for accurate diagnosis, the value of an adequately performed neurologic examination, and the important role of electrophysiologic studies in evaluating patients with carpal tunnel syndrome.

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Ratiocinating Surgeons

To the Editor: I was pleased to read Dr Stephen Leonard's comments on the subject of cognitive versus procedural physician services.[1]

His remarks made clear that the attempt to create such a dichotomy is unwise as well as false.

After all, surgeons have been known to engage in cognitive activity up to several times a day; in fact, under duress and in unguarded moments, they have even been observed to ratiocinate.

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Special Article

Uncompensated Care—The Threat and the Challenge

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Presented at the Annual Meeting of the California Medical Association House of Delegates, March 5, 1988, Reno, Nevada.

The growing crisis in uncompensated health care poses one of the most serious threats facing the medical profession today. If left unresolved, it will not only erode the health of our society and lead to an erosion of the clinical autonomy of physicians, but it will also undermine the very principles on which our health care system has been built. In addition, it will lead to increased regulation of the practice of medicine, and, quite probably, to a government-controlled health care delivery system.

To understand this threat, the challenge it poses, and our critical role in its resolution, we must first consider the evolution of our American health care system.

The health care system we enjoy in this country was founded on the principle of universal access, the idea that all Americans, regardless of their income, should have access to the health care system and to all the services it has to offer. We physicians were able to deliver on this social objective because of our fee-for-service reimbursement system and the ability to cost shift. So when the poor came for treatment, the service was rendered, and the cost was merely shifted to someone who could pay, through an incremental increase in their bill or in their insurance premium.

It is important to realize that this policy was no accident but was the result of conscious decisions in both the public and private sectors. In the public sector, the enactment of Medicare and Medicaid in 1964 extended coverage to the poor and the elderly. At the same time, there was a rapid expansion of private health insurance policies funded primarily through employment. This rapid growth of public and private third-party insurance coverage led to the belief that, in America, health care for the poor was free, when in fact it was being subsidized primarily by the government and by the business community.

Thus, we created what we felt to be an ideal health care system. It was a system with no financial restraints, where individuals had access to as much health care as they needed or wanted regardless of their income. Physicians could practice pure medicine, viewing their patients primarily from the standpoint of their health needs without concerning themselves about their ability to pay. But this system also encouraged utilization and led to the deeply held social belief in this country that health care is a right. Not surprisingly, this resulted in a dramatic increase in expenditures. The amount we spend each year on health care has grown from $75 billion in 1980 to nearly $500 billion today. More telling, however, is the growth of health care expenditures as a percentage of the gross national product: 7.4 cents on the dollar in 1970 versus about 11 to 12 cents today. If this rate of increase were to continue, by the turn of the century we would be spending 20% of the gross national product on health care and by about 2020, we would be spending 40 cents out of every dollar on health care.

Obviously, this rate of increase is not going to continue. While our health care system makes a great deal of sense in terms of a social policy, it makes very little sense in terms of an economic policy. Even a beginning student of economics recognizes that no single set of expenditures can continually grow at a rate faster than the rate of growth of the gross national product. Every dollar we spend on health care is a dollar that cannot be spent on something else. There are many other interests and priorities in which this country must invest.[1]

And while the prosperity we enjoyed over the past 20 years has allowed us to absorb these rapid increases in health care expenditures, it also masked the underlying fallacy of the way health care is financed in this country. By 1980 that mask had been stripped away when a number of factors combined to bring our ideal health care system into a collision with economic realities.

First, new medical technologies were being developed and being used—at a tremendous cost—because the system contained no financial restraints. Second, there has been a significant increase in the elderly as a percentage of the population. The elderly use more health care services than the nonelderly and have a higher incidence of chronic diseases. Both advances in medical technology and an aging population have increased the financial strain on the system.

Two additional factors forced those who had traditionally been subsidizing the cost of health care for the poor—the business community and the government—to reevaluate their ability to continue doing so. The first was the economic stagnation experienced in the United States at the beginning of this decade. While we could absorb the rapid increases in the cost of health care when the economy was growing, it was far more difficult to do so when productivity dropped. Our nation's annual productivity growth was a healthy 3% in the 1960s and 1970s but fell to 0.5% by 1979 and was actually negative in the early 1980s.

The federal budget deficit increased from about $73 billion to $211 billion in five years, and we liquidated all our foreign assets to become the largest debtor nation in the world. By the early 1980s, the government recognized that it

(Kitzhaber J: Uncompensated care—The threat and the challenge. West J Med 1988 Jun; 148:711-716)

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could no longer continue an open-ended subsidy of the cost of care for the poor without raising taxes, increasing the deficit, or making deep cuts in other domestic programs. The government became interested in cost containment to balance the budget.

At the same time, this country entered the world market. American businesses began recognizing that they were no longer competing just among themselves, as the auto industry once did; they were competing with mainland China, West Germany, Japan, Italy, and Canada. They realized they had to cut costs, particularly labor-related costs, in order to remain competitive with cheap labor industries abroad. They could not, for example, just pass the cost of health care on to their consumers and still remain competitive in a world market, particularly when American businesses had to carry the cost of health care on the books as a necessary expense and were competing with many countries that did not have to carry these costs because of nationally sponsored health care programs. The business community became interested in the need to contain costs to remain competitive.

This brought about very similar responses by both the government and the business community. The objective was simply to reduce the exposure to the cost shift and reduce the funding and subsidy of the cost of providing health care for the poor. It should be noted that the subsidy was not taken out of the system, it was merely shifted onto individuals and providers. Here is how it was done.

In 1983 the federal government enacted DRGs [diagnosis-related groups], which is a prospective reimbursement system that shifted economic risk onto providers. The federal government also began requiring first-day hospital deductibles for those on Medicare and increasing the Part B monthly Medicare premium that pays for physician services. This shifted costs onto the individuals. With Medicaid, the program for the poor, the federal government cut its match rate and shifted that to the states.

The first thing the states did was cut provider-reimbursement rates. Physicians currently average 45 to 50 cents on the dollar for taking care of someone on welfare. That pushed costs and responsibilities onto the providers. When that did not balance the budget, the states increased the requirements for Medicaid eligibility, which pushed people off the program altogether. That shifted responsibility to the individuals. In the past ten years, 800,000 women and children have been squeezed off Medicaid, and the program, which used to cover 65% of the poor, today covers less than 38%.

The private sector reacted in exactly the same way, with increased involvement in health maintenance organizations, preferred provider organizations, and other prospective managed care plans that put providers at risk. Businesses increased copayments and deductibles for their employees that shifted costs onto individuals.

The important point here is that these cost-containment actions reflected absolutely no social policy beyond that of cutting costs for the government and for the business community. There was a recognition that the amount of money that could be spent on health care for the poor was limited, but there was no consideration of the implications of those decisions on access to health care. The funding in the system was reduced but not what the public expected from the system.

Today, our health care system is in transition. We are still ostensibly committed to the principle of universal access, but now the system is driven by economic factors, not by the social factors that drove it in the 1960s and the 1970s. Providers are at economic risk. We are losing the ability to cost shift.

As I mentioned earlier, our ability to deliver on the principle of universal access has depended on cost shifting and the willingness of the business community and the government to subsidize the cost of care for the poor. While there is still supposedly a commitment to universal access, we are seeing a progressive shifting of the responsibility to pick up that cost. Between 1965 and 1980 that subsidy was borne by the government and by employers, who spread it out over taxpayers in general and over most of the workforce. Society was paying for what was essentially a social policy objective: universal access to health care.

Because of the cost-containment measures that have occurred, however, that subsidy has been shifted onto providers, who have far less ability to absorb it. What used to be subsidized care for the poor is now showing up as uncompensated care. As physicians reach a point where they cannot absorb additional uncompensated care and still pay the bills, they push the costs onto individuals. And, today, if a person does not have insurance coverage and does not have money, that person is increasingly likely to lose access to the health care system, either because providers will not accept any additional indigent patients or the patient delays treatment because of an inability to pay for it.

This has dramatically changed how health care is financed in this country. Our health care system has traditionally had a bifurcated financing mechanism. On the one side is the public system, which is Medicare and Medicaid. On the other side is the private system, which is mostly employment-based policies and some individual policies. There has always been a little gap in between where some people slipped through the cracks. But as long as the government and the business community were willing to subsidize the cost of care for the poor, that gap has been very narrow and has really contained only society's truly downtrodden.

Today, however, those two third-party payers, government and business, are trying to escape from the subsidy. As we see a reduction in government expenditures, the growth of copayments and deductibles in Medicare, and increases in Medicaid eligibility, people spill off the public side into the gap. As competition in the world market increases, as we shift from a manufacturing to a service-based economy with large numbers of low-paid, nonunionized workers without health insurance coverage, and as premium rates go up, people spill off the private side and into the gap. Today, the gap is not narrow: it contains 37 to 40 million Americans. And they are no longer just society's truly downtrodden. Of those uninsured people, 70% are working full time or part time or are dependents of someone who is working. Those in the gap are generating 75% of the uncompensated care.

Why should we be concerned about this shifting responsibility to pay for the care of the poor? We should be concerned because there are some serious social consequences affecting all of us, and some serious professional consequences affecting physicians in particular.

The first social consequence is an erosion in our commitment to universal access. Because there is a physician surplus in the country, and because care for the poor is no longer subsidized but is uncompensated, we have a very competitive, market-driven system in the provider community. And

since market systems were not designed to foster social responsibility, it should not be surprising that no one is competing to care for the poor. Public health clinics are closing. We are seeing patient dumping from hospital to hospital, physician to hospital, and between physicians. There are treatment delays. And there are a growing number of people in the gap.

That leads to the second social consequence, which is a very real and measurable deterioration of health for a growing number of Americans. We have 40,000 neonatal deaths each year from the complications of low birth weight. Two thirds of those mothers do not receive adequate prenatal care. Of the poor in America, 40% are children. Only a third of them are covered by Medicaid; the other two thirds are in the gap and are losing access to basic preventive services. We are seeing an increase in cases of pertussis and increases in pediatric nutritional problems. There is case after case of people actually dying because of a lack of access to the system—people dying of strokes because they could not get their blood pressure medication prescription refilled; people dying of heart failure and having myocardial infarctions because of a lack of routine checkups or medication; and people dying of perforated ulcers because of treatment delays.

The third and perhaps most serious social consequence is that we are mortgaging our own future. I think this is very important and would ask you to bear with me for a moment. As I mentioned, 40% of the poor in this country are children, and two thirds of them are in the gap with no insurance coverage. Also in that gap are tens of millions of young working Americans. These people constitute a large part of the shrinking workforce of tomorrow that we are expecting to fuel the economy and pay for a growing retired population. How are they going to do that in the face of $170 billion owed to foreign governments and nearly a $3 trillion national debt? How are they going to do that in the face of a $10 trillion unfunded liability, the difference between what we expect them to make and what we are planning to take out of their paychecks to pay for Medicare, Social Security, and federal pensions, most of which are automatically indexed to inflation and do not have income eligibility requirements? We are asking them to do something that we have all refused to do: to recognize that increases in personal consumption have to be balanced with increases in productivity.

In the past ten years, American workers have averaged a $3,100 increase per capita in personal consumption and only $950 of that has been paid for by increases in what each one produces. The remaining $2,150 has been paid for by cuts in domestic spending and investment and by foreign debt (P. G. Peterson, *The Atlantic Monthly,* Oct 1987, p 47). We are asking this group of people to be more productive than anyone in the history of this country and to probably take a reduction in their standard of living. Having asked them that, we are crippling them going in, by denying them access to the basic health care services they need to be healthy, productive members of the workforce. You cannot have an increase in productivity unless your workforce is healthy and well-educated. That is a very, very serious implication.

There are also some disturbing professional implications. The first is that the growing problem of uncompensated care is catching physicians between what society expects from our health care system and economic realities. When the government and the business community moved to limit their subsidy of the cost of health care for the poor, they could do so without denying access to individuals and without publicly or explicitly abandoning the idea of universal access because they shifted that subsidy onto the providers. But when physicians move to limit their exposure to this subsidy, and for exactly the same reason, they have to deny access to individuals. When physicians reach the point where they cannot absorb any additional uncompensated care, they either have to reduce the number of indigent patients they see or reduce the services they provide to those patients. In either case, that means rationing. Increasingly, physicians in this country are being forced to become the rationing instruments for a society that refuses to recognize that rationing is occurring.

That puts us in direct conflict not only with our professional ethics but with social expectations for the health care system. It casts us in a very unfavorable light. Many people still view physicians as we were seen in the halcyon days of the 1960s and 1970s when the economy was booming and incomes were rising. Most legislators are not physicians—I am the only physician in the Oregon legislature. Many legislators do not understand the relationship between cost shifting and subsidizing care for the poor, and do not understand the implications of taking cost shifting away from providers.

The thought that a wealthy profession would be denying access to the poor is unacceptable to most legislators, a fact that puts physicians in a very vulnerable position politically. As the problems of the poor intensify, state legislatures are going to begin to react. They are going to say, "If you physicians are not going to take care of the poor voluntarily, we are going to force you to do so." There are many ways that coercion can be accomplished.

As a condition of licensure, physicians can be forced to take care of a certain number of indigent patients. That bill was actually introduced in Oregon last year. A gross income tax can be applied to physicians' earnings to help pay for indigent care. That bill was introduced in Washington in 1985 and has been considered in Pennsylvania. These types of intrusive regulatory measures are being introduced in state legislatures across the country. Unfortunately, all they do is force physicians to assume the fiscal responsibility for taking care of the poor. They ignore the fact that society, while paying lip service to universal access, has made a decision to limit the amount of money that will be spent on health care. The problem remains unresolved. When someone convinces corporate America that a government-sponsored health care program will put them in a better position in terms of competition in the world market, then we will be looking at a nationalized health care program. In the short run, we are looking at increased regulation and an erosion in our own clinical autonomy.

What do we do about this problem? To solve this crisis in uncompensated care, we have to start by accepting three hard realities.

The first reality is that resources are limited. That is a difficult one for physicians to accept because they have never had to accept it. But it should be obvious to anybody who looks at the need in this country and looks at the available dollars.

We have a national debt approaching $3 trillion that we must reduce. We have a huge defense budget that has been traditionally hard to pare down. We spend $450 billion a year on Medicare, Social Security, and other federal pensions. At the same time, we are cutting aid to education and invest-

ments in roads, bridges, sewers, and water systems. We are cutting civilian research and development. We are cutting all of the things we need to increase the productivity in this country.

No one wants their personal health care expenditures cut. At the same time, however, we want to reduce government spending, we want good roads and schools, safe streets with criminals behind bars, a comfortable retirement, police protection, fire protection, clean air, and clean water. And we want to do all that, of course, with lower taxes and higher wages.

Now, obviously that does not work. There is a finite amount of money that this country can invest in health care versus the other things that we also have to invest in. Once we come to grips with the fact that there is a finite health care budget in America, then we have to decide who is going to get the service and how much service each person is going to get.

That brings us to the second reality, which is simply that the rich are always going to have access to more health care than the poor. I think that is probably all right if what the poor get is adequate and if they are all getting it. After all, one of the hallmarks of a capitalistic system is that goods and services are distributed on the basis of income, not necessarily on need or merit. We readily accept that in most instances. We do not expect public housing to look like the Ritz. We do not expect food stamps to be redeemed in expensive restaurants. But because of our concept of universal access, we have taken for granted that the poor should have access to all the health care services that are available to the rich. I would remind you that this is the only part of our system that operates on this open-ended economic principle. We have in effect rejected a multitiered system based on income, but in reality we already have that kind of a system. The rich have always been able to fly to other states and other countries for diagnostic and therapeutic modalities not available at home. The rich have had consultations and elective operations to which the poor have not had access. So what we have really is a poorly defined definition of what we think everyone has a right to and what perhaps they do not have a right to.

I think we would all agree that everyone should have a right to prenatal care, but we may argue whether or not the public should pay for an elective face-lift for everybody on welfare. The question becomes much more difficult, however, when we are trying to balance a transplant versus prenatal care.

We need a better definition of adequate health care to address that question. If we know resources are limited, if we know people with high incomes can buy more health care than people of lower incomes, and if we know that society cannot buy everything for everyone who might benefit from it, we must consciously and responsibly decide what level of health care everybody should get. That means defining adequate health care and brings us to the third reality.

The third reality is the inevitability of rationing. This is also a very difficult concept for physicians to come to terms with, but when you define adequate health care, you also define what is more than adequate. And that provides the basis for the explicit rationing of health care. Before we overreact to this reality, I would suggest that rationing already exists in our system. We clearly already ration by income and by transportation barriers. More important, however, we ration inadvertently through legislative decisions because we lack any policy to guide how our health care dollars are spent. Rationing is the result of limits. If there is a limited amount of money in the health care budget and it is spent on one set of services, it is not available to be spent on another set of services. That is rationing.

Consider how this is being done today. Almost $2,000 per capita is spent each year on health care in America, far more than any other country in the world. Yet our wellness, as measured by morbidity and mortality statistics, is not significantly better than that in England, which spends $500 per capita, or even Singapore, which spends only $200 per capita (R. Lamm, "The Ten Commandments of Health Care," speech given at the Midwest Health Conference, Kansas City, Mo, March 28, 1988).

Why? Because we have no policy to guide how we spend our health care dollars. We are spending huge sums on some and we are spending virtually nothing on others. We spend more per capita on health care than any other country in the world, yet 37 million Americans have no coverage and many of them are losing access to the system. We spend $3 billion a year on neonatal intensive care while denying prenatal care to hundreds of thousands. We spend $50 billion a year on people in the last six months of their lives while closing pediatric clinics.[2]

That is like having someone in charge of a corporate truck fleet who adopts a policy that the oil in the trucks will not be changed until the engine blocks melt. The trucks won't be maintained but will be serviced only when there is a major breakdown. I doubt if you would endorse this policy for your car, nor would you employ anyone who did, but that is exactly how we spend health care dollars in this country. Rather than spending money on prenatal care, we spend it on neonatal intensive care. Rather than treating hypertension, we treat people who have had strokes. We are rationing by default, unguided by any social policy. It is inequitable, inefficient, and we are wasting millions of dollars and thousands of lives. The reason we are rationing implicitly as opposed to explicitly is because we do not want to come to grips with our own limits.

To solve the problem of uncompensated care, with all of its ominous implications for society and for physicians, we have to recognize that our health care system is indeed in flux and that we have to build a new system based on the three realities that I mentioned: limited resources, acceptance of the fact that the rich will always be able to buy more health care than the poor, and the need for rationing.

We have to recommit ourselves to universal access—not universal access for everyone to everything—rather, universal access for everyone to an adequate level of health care. That will put our system back on a sound economic foundation. It also means that we are going to end up in this country with a three-tiered system of delivery. In reality we already have a nondefined, implicit multitiered system: the medically indigent, Medicaid, workers with insurance, the wealthy. What I am suggesting is that we stop pretending it doesn't exist, accept its inevitability, and take steps to make it work equitably and efficiently. This would mean a government-sponsored tier for the poor, a tier that the business community funds for those who are working, and a traditional fee-for-service tier for those who wish to buy additional health care services.[3]

I want to reiterate one point. The government has a responsibility, in my mind, to pay for the poor but not for the elderly unless they are also poor. The government should pay

for the poor regardless of their age. There is no reason Lee Iacocca needs Medicare, or Johnny Carson, or even my parents. Government-subsidized health care programs should have income eligibility requirements.

This is important because it is at the first, or public, tier that we have to come to grips with rationing. It is at this tier that we must set the socially acceptable minimum level of health care for this country. How do we get there?

Let me describe what is being done in Oregon, where we are attempting to resolve this problem. There are three elements involved: first, a clear social policy; second, a definition of adequate health care; and third, a universal insurance system to guarantee that people get access to that care.

Because of my time constraint, I will only cover the first two elements. Concerning universal health insurance coverage, however, let me say that while it is an essential component of the final solution, it is putting the cart before the horse. We need to recognize that the objective of our social policy of the 1960s and 1970s was, in fact, universal access. One of the reasons we are in trouble today is that we were, in the short run, able to cover everybody for almost everything. But unless we first define the level of care for which people are universally covered, we still have an open-ended system that we cannot afford.

Therefore, we first need a clear social policy to ensure that we spend our limited health care dollars in a way that is efficient and equitable. In Oregon we have made an attempt to recognize our limits and to adopt such a policy. In the past legislative session, we discontinued funding for heart, pancreas, bone marrow, and liver transplants for people on welfare and used that money to extend preventive and prenatal services to a far larger group of people who had been in the gap. This constituted an explicit rationing decision. Let me go over the issue we were dealing with because, I assure you, it has not been an easy one to defend, politically or as a physician, although I firmly believe that it was the correct decision given the reality of limited resources.

The question was not whether transplants have merit; clearly they do. The issue was not whether in the short run we could find some additional money to buy a few more transplants for people on public assistance; clearly we could have. The issue was simply that if we were going to put additional money into health care, where was the best place to spend the next available dollar? Did it make more sense and was it a better use of limited public funds to buy high-tech services for a group of people (those on Medicaid) who already had access to virtually everything available in the private sector, or to extend services to a larger number of people who were in the gap, many of whom did not have access to any health care whatsoever?

We felt it made more sense to serve the larger number of Oregonians. Thus, the policy adopted in Oregon is one of universal access to adequate health care, and we have made that the first priority for spending the additional dollars that we can get into our health care budget. That still leaves the second element: defining adequate health care. Oregon's definition at this point does not include major organ transplants because we have made a decision that they are of a lower priority than preventive care. But we do need a more complete decision.

Before I describe to you the process we are using in Oregon to arrive at that decision, let me say that once you get a definition of adequate health care and array your health care services on a priority basis, you are changing, in a fundamental way, the nature of the rationing debate. The rationing debate traditionally has an individual focus, and it goes like this. We have one heart and three potential recipients. Do we give that heart to a 17-year-old unwed mother of three on welfare, do we give it to a 35-year-old man serving time for rape and armed robbery, or do we give it to a 40-year-old corporate executive?

This scenario raises the kinds of imponderable ethical and moral questions that society, almost by definition, cannot resolve on an individual basis. But once we develop a definition of adequate and array our health care services in a priority order, we shift that debate from an individual focus to a societal focus. We are no longer debating which service should be given or denied to which person, we are debating which priority of funding should be given to each service, given the reality of limited resources. Because society has made the decision to limit the amount of money it spends on health care, society needs to make the decision on how to spend that money. In addition to providing basic health care to a far larger number of people, this approach also takes physicians out of the squeeze and allows them to continue to be patient advocates. They can continue to do everything they can possibly do for their patients within the context of the resources that society has made available.

How do we get to this definition of adequate? There are really three steps. The first and probably the most difficult is building a consensus. In Oregon we are working with a group called Oregon Health Decisions, founded in 1982 by Ralph Crawshaw, MD, a Portland psychiatrist. It is a private, nonprofit group dedicated to educating Oregonians on the health policy choices and confronting them with the consequences of those choices. It was the first such group in the country. Now 14 states have similar organizations, including an active one in California.

We have appointed a steering committee of which I am the chair. We are breaking down everything on which Oregon currently spends its health care dollars. We are making a decision package for each service with a summary document that describes the number of people getting the service and the cost, the number of people not getting the service and the economic and health implications of not giving them that service, and then the cost to extend the service to everybody in the unmet-need population.

The plan over the next few months is to arrange this list in a tentative priority order and take it out to town hall meetings around the state of Oregon where citizens can actually get involved in working through the trade-offs and choices necessary to set up a priority list of health care choices, given the fact of limited resources. We will bring that information together this fall to generate a final list that will be submitted to the legislature.

Once the health care resources are arrayed in that kind of priority list, we come to the second step, which is to integrate this information with the legislative budget process. This requires that funding go to the first item on the priority list for everybody in the population for whom the state has responsibility. Going down the list, the second item is fully funded before moving to the next, then the third, the fourth, and so on, until the available money is exhausted.

This process puts accountability into the system. If, for example, a state legislature decides to cut $20 million out of the health care budget, it will no longer be an abstract ac-

counting exercise but will mean deleting specific services for specific individuals off the bottom of the priority list. The debate becomes far more focused. If someone wants to re-fund the transplant program, clearly they either have to knock something else off the priority list—and they must make a choice, a clinical choice and a political choice, between those two health care services—or they have to rob another program or raise more money (increase taxes).

The final point with this type of system is that if it is done on the basis of sound clinical information, money can actually be saved. A California obstetrics-access study suggested that the cost of treating an indigent woman for prenatal care and delivery was $1,000 and the cost of treating a low-birthweight infant was $28,000, up to six figures. The study suggested that if prenatal care were provided to all the indigent women who needed it, $22 million a year could be saved in the health care system. That is money that can be used to add services on the priority list, such as major soft organ transplants. It could be used to raise provider reimbursement to a reasonable level and thus remove the current economic disincentive to treat the medically indigent and those on Medicaid, or it could be used for roads. In any event, the debate becomes much clearer and more focused. Accountability is inescapable.

What is the role of physicians in resolving this problem? The first and most significant role we have to play is that we must come to grips with our own limits. We have to recognize that health care resources in America are, in fact, limited. If the leadership of professional medical organizations is going to publicly refuse to recognize that health care resources are limited, how can we expect the public to accept that, and how can we expect state legislatures to recognize that as well? If we are not willing to recognize this ourselves, we are inviting all of the ominous social and professional consequences that uncompensated care is bringing our way. As a first priority, therefore, physicians must recognize and accept limits in health care, express that view publicly, and talk it over with each other and with their patients.

Second, through our professional organizations we need to adopt policies on how to expend limited public health care dollars. Your society or association may already have such a policy but, if not, I would suggest one that states that the first priority should be to extend an adequate level of care to everyone. Then, and only then, should we indulge ourselves in the debate over how to spend what is left in the budget.

This means, of course, that we must also get involved in the definition of adequate. Physicians are really the only group in this country with the qualifications to provide sound clinical information to the state legislature. We need to say: "Yes, we are going to have to ration health care in this country. It is inappropriate and unethical for physicians to do the rationing; society needs to do it. And if you, the legislature, are going to ration health care, here is a list of priorities that make sense clinically. This makes sense in terms of marginal costs and marginal benefits. This makes sense in terms of probable outcome." Physicians have to provide that input. Then we have to support legislative decisions that make responsible resource allocation choices. We have to do that publicly, in our community, and at the legislative level.

This, then, is the threat and the challenge of uncompensated care. The solution, I believe, is a partnership between public policymakers at the state legislative level and leadership in the medical community. If left unresolved, this problem of uncompensated care is going to result in an erosion in our social commitment to universal access to health care and a deterioration of health for a growing number of Americans, with very serious social and economic consequences. It is going to put physicians in conflict with their professional ethics and with what society expects from the health care system, which will lead to regulation, an erosion of clinical autonomy, and very likely a nationally controlled health care delivery system. We need not accept this outcome. In fact, we cannot accept this outcome. With the active involvement and leadership from the medical community, we can meet this challenge and restore some rationality and equity and economic stability to our health care system.

I ask you to join me in meeting that challenge.

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Topics in Primary Care Medicine

Health Issues of Homeless Persons

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"Topics in Primary Care Medicine" presents articles on common diagnostic or therapeutic problems encountered in primary care practice. Physicians interested in contributing to the series are encouraged to contact the series' editors.

BERNARD LO, MD
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Series' Editors

Homelessness implies not only a lack of shelter, but also a degree of social isolation. Homelessness is essentially a socioeconomic problem; the homeless also have a high prevalence of medical and mental health problems and frequently use public emergency departments. We review the demographics and causes of homelessness and the diseases that homeless people are commonly afflicted with and discuss strategies to manage their problems.

Demographics and Causes

Although the homeless population has always been more diverse than such stereotypes as the alcoholic men who frequented the flophouses and missions of skid row, the ranks of the homeless have been swelled recently by women, families, youth, seniors, disabled persons, veterans, and people with the acquired immunodeficiency syndrome (AIDS) or AIDS-related conditions (ARC). Estimates of the number of homeless nationwide range from 350,000 to 3 million. In San Francisco, there are about 5,000 to 6,000 homeless people on any given night. Available data and anecdotal evidence suggest some general characteristics. The average age is about 37 years. Most are men, although women constitute about 20%. Ethnic minorities, particularly blacks, Latinos, and Native Americans, are overrepresented, together composing about half of the homeless population. Between 20% and 40% of the homeless have some education beyond high school.

The factors contributing to homelessness can be as diverse as the populations affected. Many are homeless due to the combined forces of economic setback, a lack of affordable housing, and the failure of the "social safety net." In this group are the physically disabled or chronically ill, the elderly on fixed inadequate incomes, or able-bodied single adults receiving General Assistance who often find it impossible to maintain stable housing on their limited monthly grant. Many of the new homeless have experienced severe disruptions in their lives, such as women who have fled abusive partners, homeless youth who often have also left abusive home situations, the 30% to 40% who are veterans—half from the Vietnam era—or people with AIDS or ARC.

Finally, there is a group of people whose homelessness is often linked to a chronic condition, such as alcoholism or mental illness. Deinstitutionalization and inadequate community mental health programs have left many to fend for themselves on the streets. This group generally receives the most attention, primarily because alcoholism and mental illness are caught up in the polemics over the causes of homelessness and because they are very visible on the city streets. Neither condition by itself, however, is an explanation for homelessness, and the daily uncertainties related to food, shelter, and security dramatically diminish the possibilities of recovery.

Health Problems

Living on the streets exposes people to extremes in temperature. They are often not protected from rain or snow. Their clothes, particularly their shoes, may be ill fitting. Access to showers and clean clothes is restricted. Sleeping arrangements are often bizarre. All of one's possessions must be carried, and shelters and dining rooms are usually crowded so that lining up for hours is a standard part of one's day. Health problems are exacerbated by the street life. Homeless persons often come late to medical attention and are less likely to return for follow-up visits. The homeless have a high prevalence of physical and mental illnesses and are frequent users of emergency departments. They are often admitted for far-advanced conditions that could have been prevented or treated earlier as outpatients.

Foot Problems and Cellulitis

Foot problems are common because the homeless spend many hours standing in lines or walking. Secondhand, worn thin, or ill-fitting shoes cause calluses or abrasions. Fungal foot infections are common. The inability to lie down leads to edema and venous stasis that, when combined with insect bites or abrasions, may lead to ulceration and cellulitis. Hospital admissions for the treatment of cellulitis or deep ulceration are common. In a chart review, it was found that two thirds of homeless persons presenting with lacerations came to medical attention more than 24 hours after the injury, and

(Wlodarczyk D, Prentice R: Health issues of homeless persons. West J Med 1988 Jun; 148:717-719)

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less than 30% returned for follow-up wound care. When follow-up is doubtful, adhesive wound closure, such as Steristrip, preceded by copious irrigation, may lead to fewer wound complications than when sutures are left in too long. Medicated bandages, such as Unna's boots, may be used to facilitate the healing of leg ulcers and may be left on for a week rather than prescribing daily wet to dry dressing changes. A solution of one part bleach to ten parts water applied to bathroom floors and shower stalls in shelters can inexpensively and effectively kill common fungi that can cause foot infections. Heavy-duty nail clippers need to be available to cut overgrown, thickened nails.

Upper Respiratory Tract Infections

Common colds and other respiratory tract infections spread easily in overcrowded shelters and food lines. The inability to rest and the high rate of smoking exacerbate the severity of these diseases. Annual influenza vaccination should be offered to all homeless persons because of the ease of spread and their inability to rest and recuperate in the shelters or on the street. Smoking cessation should be recommended just as it should to the general public.

Tuberculosis

The prevalence of tuberculosis is greatly increased among the homeless. The rate varies from epidemic proportions in New York to lower rates in other cities. Boston has had an outbreak of isoniazid- and streptomycin-resistant cases. Tuberculosis is an important problem among the homeless and shelter staff. Thorough contact investigation is important and effective when a case is detected because crowded conditions facilitate infection transmission. Compliance with random screening with purified-protein-derivative skin tests is poor but should be done to offer prophylaxis to this high-risk, relatively young group. In cases of possible tuberculosis, sputum specimen collection and chest x-ray films should be done on site, and the acid-fast bacilli smear and chest x-ray film should be reviewed before the person leaves the site. Once a case of current tuberculosis is diagnosed, the treatment should be supervised daily with the aid of the city or county tuberculosis control program, and the person should be moved into a single-room residence. The use of a four-drug, six-month regimen is more likely to be completed than longer regimens. Shelter staff need to be educated about tuberculosis and screened for infection. Adequate ventilation, less crowding, and ultraviolet lights should be helpful in reducing disease transmission in the shelters.

Infestations

Body and head lice and scabies are frequent problems. Treatment is difficult because of reexposure in the shelters and a lack of facilities to shower and wash one's clothes. Insect bites may lead to local abscesses, impetigo, cellulitis, and occasionally septicemia. Local and systemic toxic reactions, including seizures, may occur in persons who have been treated repeatedly and for prolonged periods with lindane. Lindane lotion is the treatment of choice for scabies. For head lice, a pyrethrin or lindane shampoo can be used. Careful combing with a stiff, fine-toothed comb will remove residual nits. Body lice can be treated by simply washing with soap and water and hot water washing of clothes and bedding. When infestation is extensive, lindane shampoo to the entire body excluding the eyes and mucous membranes will improve the outcome. Dispensing a pediculocide to a person who does not have a change of clothes or access to shower facilities is likely to be futile. The health care provider needs to know where those resources can be found or provide them on site.

Hypothermia

Persons living on the streets are at an increased risk for hypothermia, particularly if their consciousness is impaired (from alcohol or drugs), if they are lying on concrete or other surfaces that conduct body heat away rapidly, or are wet from the weather or incontinence. Temperatures do not have to be below freezing to cause hypothermia.

Substance Abuse

Most of the data on the prevalence of alcohol and drug abuse is from studies of male shelter users in skid row areas, and the rate is high. Detoxification and 28-day programs provide islands of sobriety, but usually the person is deposited back on the streets homeless and jobless with little likelihood of remaining sober. Longer term programs that deal with the other social and economic problems do better. All drug abusers need to be taught AIDS and other infection risk reduction. For those unwilling to stop intravenous drug abuse, small bottles of household bleach with instructions on how to clean their "rig" can be provided and may reduce the risk of infection. The use of condoms needs to be promoted and condoms provided. As the AIDS epidemic increasingly affects intravenous drug abusers, the number of persons with AIDS or ARC who are living on the streets is expected to grow.

Mental Health

Large numbers of mentally ill persons live on the streets and in shelters. They are often visible, leading to the stereotypic perception that most homeless persons are mentally ill. Data suggest that the incidence of significant mental health problems among the homeless is in the 30% to 40% range. Among the homeless mentally ill, women are overrepresented. Concurrent physical health problems are reported by half to a third of the homeless mentally ill. The mentally ill are often robbed or assaulted because they are among the easiest prey. The sickest of the mentally ill are the least likely to seek mental health care and are likely to end up in involuntary incarceration.

Deinstitutionalization of the mentally ill in the 1960s and 1970s shifted the focus of treatment from the hospital to the community, but community-based housing and care were never adequately developed. The streets became the repositories for many of those who were least able to care for themselves. Treatment of the homeless mentally ill is complex, often depending on resources that are not particularly tailored to the population. It is clear, for example, that traditional mental health services must be supplemented by affordable housing with on-site social support to enable people to live at the highest level of independence possible. In addition, a system of case management can coordinate mental health, entitlements, housing, transportation, and other services that are critical to the overall functioning of clients. The appropriate use of outpatient treatment and other mental health services can only be realized when other needs for security and support are taken care of.

Trauma

Trauma is a significant cause of morbidity and mortality among the homeless. Homeless women are at an increased risk of sexual assault.

Other Chronic Diseases

Hypertension, diabetes mellitus, and chronic obstructive pulmonary disease probably occur no more frequently than in the general population. Optimal control of these problems is made difficult if not impossible by the lack of stable housing, the inability to select one's diet, and difficulties in storing and taking medication on schedule. Treating diabetes is particularly difficult because the time and composition of meals is not under a homeless person's control. Insulin syringes have a high street value, and diabetic persons are often targeted for robbery. The temptation to sell the syringes is also high.

Populations With Special Needs

Youth. Homeless and runaway youth can no longer rely on their families for financial and emotional support, and they are ineligible for many entitlements programs. Some turn to "hustling" (prostitution) to get by, placing them at high risk for sexually transmitted diseases. Suicidal ideation and histories of suicide attempts are common. Active outreach programs that offer condoms and bleach, nonjudgmental counseling, meal vouchers, and a place to stay can be a first step in getting homeless youth off the streets.

Families. Homeless families are commonly headed by women. Some have a long history of residential instability, while others have only recently lost their housing. The mothers in many cases have fled abusive partners, have poor job skills, and lack supportive relationships. The children of homeless families are usually below grade level in school and often suffer from learning disabilities and depression. Nutrition is frequently inadequate. Successful programs must combine counseling and rehabilitative services with stable income and housing.

Barriers to Health Care

Homeless people face a variety of barriers to health care. Health services available to the homeless are limited, and homeless people may find it difficult to identify the appropriate place of care. Public clinics and public hospital emergency departments may be geographically distant and transportation unaffordable. Long waits can sometimes mean that a meal or a shelter bed is lost. Complicated registration processes and even minimal patient fees present further sources of discouragement. The lack of a sensitive and sympathetic staff, or the inability of a single service site to address the wide range of problems experienced by homeless people, can pose additional barriers.

In some cases, health care problems are denied or are given a low priority by homeless persons. A lack of understanding of their health needs, the fear of losing control over their daily life and possessions, self-destructive behavior, embarrassment about their personal hygiene or clothing, and the need to attend to other survival needs may cause them to come to medical attention only when their disease is far advanced. Many homeless have had dissatisfying experiences with the health care system in the past and are skeptical that going again will do any good. For some, life on the streets has led to a general skepticism about institutions.

Primary Care Providers and the Homeless

Providers must first be nonjudgmental and establish confidence and mutual trust. Existing medical, mental health, and social work services must be actively coordinated. A forgiving schedule and allowing drop-in visits are essential for accommodating the vagaries of street life, although keeping appointments might become part of a rehabilitative regimen. Early intervention and continuity of care are best accomplished through ready availability, active outreach, and persistent follow-up. Working with homeless people can frequently be labor-intensive and frustrating. It involves advocacy for entitlements, housing, employment, and needed health care services as integral components of a therapeutic intervention. Experienced staff sensitive to the needs of homeless people must work with hospital discharge planners and other health care providers to ensure that care is given in a manner that is appropriate to the life circumstances of homeless people.

Conclusions

The homeless in America are a large, diverse, and growing group who have special health and social service needs. Although it is important to avoid the short-sightedness of institutionalizing homelessness, there is nevertheless justification for developing services that specifically target homeless people as part of the overall strategy for confronting homelessness and its consequences. Those services must be tailored to the actual life conditions of homeless people, they must acknowledge that medical problems are part of a much broader set of circumstances, and they must be provided in a sensitive and committed manner.

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Commentary

Thoughts From Attending a Continuing Medical Education Meeting

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The image I see in the mirror every morning as I shave, with all its wrinkles and actinic keratoses, suggests that I have suffered from an addiction, not to recreational chemicals, but to a more benign and enjoyable external irritant—sunlight. I will admit it; I have been a life-long sun worshipper.

Until recently I blithely ignored this addiction and the harm it has wrought to my epidermis. Then, early this year, along came that article in JAMA, which the media immediately accepted as giving approval to that good, old acne remedy, Retin-A, as a cure for wrinkles. It did not take my patients long to put in requests for that miracle drug.

I had the good fortune shortly thereafter to listen to the advice given by two speakers at a dermatologic seminar. They gently chided us, a group of non-dermatologists, for our failure to instruct patients in skin care and the prevention of sun damage.

I resolved I would take back to my practice the pearls of wisdom these speakers had given me. Now, as summer approaches, these are the precious educational gems that I hope to pass on to my patients.

Remember that sunlight is a very powerful source of ultraviolet irradiation. When you are out in the sun, you are being bombarded by not one but three types of ultraviolet rays, each with different strengths and characteristics. They are labelled UVC, UVB, and UVA.

UVC is the most damaging type of ultraviolet light, valuable only for its use in germicidal lamps. So far our little planet Earth is still shielded from these rays by a layer of ozone.

UVB is the sunburn sunlight. It is what got me into trouble. Sure, it gives us a tan, but lifelong exposure produces the aging of the skin that results in wrinkles.

UVA is the so-called safe sunlight touted by the tanning parlors. While it tans without burning, except in high doses, it does wrinkle and leatherize the skin. Even though in itself it is not a strong carcinogen, it may secondarily increase the carcinogenic effect of UVB.

In making my pitch to my sunworshipping patients I will remind them that none of us is immune to skin cancer. Perhaps they would even be willing to enter into a compromise if I were to offer them hints on how to tan more safely.

The first rule I would give to any patient willing to listen would be this: If you absolutely must use a tanning booth to achieve a tan, do not overdo it. Your objective should be to stimulate the melanocytes to go to work, but you do not need to induce a burn to achieve that.

The second bit of advice would have to do with timing. We know that the maximum penetration of UVB into our atmosphere occurs when the sun is high in the sky. For instance, on the longest, sunniest day of the year, June 20th, 60% of all the UVB rays will strike the earth's surface between 10:00 AM and 2:00 PM. If at all possible, stay out of the sun during those hours.

Be aware of your sun sensitivity levels, and make use of a sunscreen of the proper strength. If you have the olive skin of a toreador, a sunscreen with a sun protective factor (SPF) of five may suffice. But if my patient is fair-haired or a redhead, I would suggest a sunscreen of SPF 15 or higher.

Then, if my patients still insist on being helio heroes by hitting the beach between ten and two, I will insist they allow themselves no more than 15 or 20 minutes of unprotected sunning, and that they then gob on the sunscreen and don their hats and shirts. And cover their insteps. That night they will sleep better, and theirs will be a better tan.

I will go on to warn my older patients (we like to be called mature Americans) that the skin of the aging scalp is more likely to burn than to tan. I can speak from my own experience with a tender, sun-burned, blistered forehead.

Here are three additional pearls I will offer to my patients: Suntan oil enhances ultraviolet penetration, thereby increasing the likelihood of a bad burn. Secondly, wearing a wet T-shirt, rather than giving protection, will also increase the chance of a burn. And third, a person using certain medications may be surprised by a quick and painful burn. Tetracycline, sulfa, nonsteroidal anti-inflammatory drugs, and thiazides, for example, can greatly increase photosensitivity.

Finally, here is one last pearl, and one of the most important ones I can give my patients. Just as UVB sunlight can blister bald pates and tender insteps, so, too, can these rays blister our eyeballs. There is reason to think that ultraviolet sunlight plays a major role in the formation of cataracts.

Lenses that filter out harmful ultraviolet rays are now available, and I will suggest to my patients that their present sunglasses may already be fitted with such lenses. To find out, they can check the temple piece or the bow to see if Z-80.3 is imprinted there. Those numerals would indicate that their corneas are being given a modicum of protection.

And so, my final advice to my patients will be: Tan your hide, if you must, but be smart and do it in moderation. And, please, for your good sight's sake, do not cook your corneas!

(Fox ERW: Thoughts from attending a continuing medical education meeting. West J Med 1988 Jun; 148:720)

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Precautions: *General*—1. Symptomatic response to nizatidine therapy does not preclude the presence of gastric malignancy.

2. Because nizatidine is excreted primarily by the kidney, dosage should be reduced in patients with moderate to severe renal insufficiency.

3. Pharmacokinetic studies in patients with hepatorenal syndrome have not been done. Part of the dose of nizatidine is metabolized in the liver. In patients with normal renal function and uncomplicated hepatic dysfunction, the disposition of nizatidine is similar to that in normal subjects.

Laboratory Tests—False-positive tests for urobilinogen with Multistix® may occur during therapy with nizatidine.

Drug Interactions—No interactions have been observed between Axid and theophylline, chlordiazepoxide, lorazepam, lidocaine, phenytoin, and warfarin. Axid does not inhibit the cytochrome P-450-linked drug-metabolizing enzyme system; therefore, drug interactions mediated by inhibition of hepatic metabolism are not expected to occur. In patients given very high doses (3,900 mg) of aspirin daily, increases in serum salicylate levels were seen when nizatidine, 150 mg b.i.d., was administered concurrently.

Carcinogenesis, Mutagenesis, Impairment of Fertility—A two-year oral carcinogenicity study in rats with doses as high as 500 mg/kg/day (about 80 times the recommended daily therapeutic dose) showed no evidence of a carcinogenic effect. There was a dose related increase in the density of enterochromaffin-like (ECL) cells in the gastric oxyntic mucosa. In a two-year study in mice, there was no evidence of a carcinogenic effect in male mice, although hyperplastic nodules of the liver were increased in the high dose males compared to placebo. Female mice given the high dose of Axid (2,000 mg/kg/day, about 330 times the human dose) showed marginally statistically significant increases in hepatic carcinoma and hepatic nodular hyperplasia with no numerical increase seen in any of the other dose groups. The rate of hepatic carcinoma in the high dose animals was within the historical control limits seen for the strain of mice used. The female mice were given a dose larger than the maximum tolerated dose, as indicated by excessive (30%) weight decrement compared to concurrent controls, and evidence of mild liver injury (transaminase elevations). The occurrence of a marginal finding at high dose only in animals given an excessive, and somewhat hepatotoxic dose, with no evidence of a carcinogenic effect in rats, male mice, and female mice (given up to 360 mg/kg/day, about 60 times the human dose), and a negative mutagenicity battery is not considered evidence of a carcinogenic potential for Axid.

Axid was not mutagenic in a battery of tests performed to evaluate its potential genetic toxicity, including bacterial mutation tests, unscheduled DNA synthesis, sister chromatid exchange, and the mouse lymphoma assay.

In a two-generation, perinatal and postnatal, fertility study in rats, doses of nizatidine up to 650 mg/kg/day produced no adverse effects on the reproductive performance of parental animals or their progeny.

Pregnancy—Teratogenic Effects—Pregnancy Category C—Oral reproduction studies in rats at doses up to 300 times the human dose, and in Dutch Belted rabbits at doses up to 55 times the human dose, revealed no evidence of impaired fertility or teratogenic effect, but, at a dose equivalent to 300 times the human dose, treated rabbits had abortions, decreased number of live fetuses, and depressed fetal weights. On intravenous administration to pregnant New Zealand White rabbits, nizatidine at 20 mg/kg produced cardiac enlargement, coarctation of the aortic arch, and cutaneous edema in one fetus and at 50 mg/kg it produced ventricular anomaly, distended abdomen, spina bifida, hydrocephaly, and enlarged heart in one fetus. There are, however, no adequate and well-controlled studies in pregnant women. It is also not known whether nizatidine can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Nizatidine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers—Nizatidine is secreted and concentrated in the milk of lactating rats. Pups reared by treated lactating rats had depressed growth rates. Although no studies have been conducted in lactating women, nizatidine is assumed to be secreted in human milk, and caution should be exercised when nizatidine is administered to nursing mothers.

Pediatric Use—Safety and effectiveness in children have not been established.

Use in Elderly Patients—Ulcer healing rates in elderly patients are similar to those in younger age groups. The incidence rates of adverse events and laboratory test abnormalities are also similar to those seen in other age groups. Age alone may not be an important factor in the disposition of nizatidine. Elderly patients may have reduced renal function.

Adverse Reactions: Clinical trials of nizatidine included almost 5,000 patients given nizatidine in studies of varying durations. Domestic placebo-controlled trials included over 1,900 patients given nizatidine and over 1,300 given placebo. Among the more common adverse events in the domestic placebo-controlled trials, sweating (1% vs 0.2%), urticaria (0.5% vs <0.01%), and somnolence (2.4% vs 1.3%) were significantly more common in the nizatidine group. A variety of less common events was also reported; it was not possible to determine whether these were caused by nizatidine.

Hepatic—Hepatocellular injury, evidenced by elevated liver enzyme tests (SGOT [AST], SGPT [ALT], or alkaline phosphatase), occurred in some patients possibly or probably related to nizatidine. In some cases, there was marked elevation of SGOT, SGPT enzymes (greater than 500 IU/L), and in a single instance, SGPT was greater than 2,000 IU/L. The overall rate of occurrences of elevated liver enzymes and elevations to three times the upper limit of normal, however, did not significantly differ from the rate of liver enzyme abnormalities in placebo-treated patients. All abnormalities were reversible after discontinuation of Axid.

Cardiovascular—In clinical pharmacology studies, short episodes of asymptomatic ventricular tachycardia occurred in two individuals administered Axid and in three untreated subjects.

Endocrine—Clinical pharmacology studies and controlled clinical trials showed no evidence of antiandrogenic activity due to Axid. Impotence and decreased libido were reported with equal frequency by patients who received Axid and by those given placebo. Rare reports of gynecomastia occurred.

Hematologic—Fatal thrombocytopenia was reported in a patient who was treated with Axid and another H_2-receptor antagonist. On previous occasions, this patient had experienced thrombocytopenia while taking other drugs.

Integumental—Sweating and urticaria were reported significantly more frequently in nizatidine than in placebo patients. Rash and exfoliative dermatitis were also reported.

Other—Hyperuricemia unassociated with gout or nephrolithiasis was reported.

Overdosage: There is little clinical experience with overdosage of Axid in humans. If overdosage occurs, use of activated charcoal, emesis, or lavage should be considered along with clinical monitoring and supportive therapy. Renal dialysis for four to six hours increased plasma clearance by approximately 84%.

Test animals that received large doses of nizatidine have exhibited cholinergic-type effects, including lacrimation, salivation, emesis, miosis, and diarrhea. Single oral doses of 800 mg/kg in dogs and of 1,200 mg/kg in monkeys were not lethal. Intravenous LD_{50} values in the rat and mouse were 301 mg/kg and 232 mg/kg respectively. PV 2091 AMP [041288]

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CONTINUING MEDICAL EDUCATION

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NEW MEXICO

Information, requests for accreditation and items to be listed should be sent to the chairman of the CME Committee, New Mexico Medical Society, 303 San Mateo NE, Suite 204, Albuquerque, NM 87108 at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 266-7868.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

July 7-9—**New Mexico Ophthalmological Society Annual Meeting.** Eldorado Hotel, Santa Fe. Thurs-Sat. Contact: Donald J. Ham, MD, 1124 10th, Alamogordo 88310. (505) 434-1200.

July 18-21—**Ruidoso Family Practice Seminar.** Inn of the Mountain Gods, Mescalero. Mon-Thurs. Contact: NM Chapter, AAFP, PO Box 23070, Albuquerque 87192. (505) 298-5300.

July 22-24—**Diagnosis and Management of Arrhythmia.** Presbyterian Heart Institute, Albuquerque. Fri-Sun. Contact: Barry Ramo, MD, (505) 841-1065/(505) 242-2796.

July 28-30—**General Surgical Update.** Hilton Hotel, Albuquerque. Thurs-Sat. Contact: UNM SOM, Office of CME, (505) 277-3942.

August 5-6—**Santa Fe Cardiology Update.** Fri-Sat. Contact: New Heart Program, (505) 255-8474.

September 8-10—**Concepts & Controversies in Perinatal Care.** Albuquerque. Thurs-Sat. Contact: UNM SOM, Office of CME, (505) 277-3942.

September 22-24—**Primary Care Update '88.** UNM Conference Center, Albuquerque. Thurs-Sat. Contact: UNM SOM, Office of CME, (505) 277-3942.

October 6-8—**Management of Radiation Accidents.** Sheraton Old Town Hotel, Albuquerque. Thurs-Sat. Contact: UNM SOM, Office of CME, (505) 277-3942.

October 18-21—**Epidemiologic & Methodologic Problems in Determining Nutritional Status of Older Persons.** Sheraton Old Town Hotel, Albuquerque. Tues-Fri. Contact: UNM SOM, Office of CME, (505) 277-3942.

October 28-29—**New Mexico Medical Society Interim Meeting** and **Loss Control Seminar,** Physicians Mutual Liability Insurance Co. Journal Center Pyramid Holiday Inn, Albuquerque. Fri-Sat. Contact: New Mexico Medical Society, 303 San Mateo NE, Albuquerque 87108. (505) 266-7868.

November 11—**New Mexico Pediatric Society.** Inn of the Mountain Gods, Ruidoso. Fri. Contact: Marilyn Stark, (505) 265-7431.

December 1-3—**American College of Physicians—New Mexico Scientific Meeting.** Hilton Hotel, Albuquerque. Thurs-Sat. Contact: UNM SOM, Office of CME, (505) 277-3942.

December 9-10—**Trauma Update '88.** Clarion Four Seasons Hotel, Albuquerque. Fri-Sat. Contact: UNM SOM, Office of CME, (505) 277-3942.

UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the CME office of the Utah Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. They also must meet the definition of Utah Approved CME Credit for the purpose of medical license reregistration in Utah. Accredited institutions wishing to list AMA Category 1/Utah Approved CME courses here should send information at least two months in advance to the Office of Continuing Medical Education, 540 East Fifth South, Salt Lake City, Utah 84102; or phone (801) 355-5290. For information on CME accreditation or on the CME requirements of the Utah Physicians' Licensing Board, please write the CME office at the above address.

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1. For therapeutic use in patients with hypokalemia with or without metabolic alkalosis, in digitalis intoxication and in patients with hypokalemic familial periodic paralysis.
2. For the prevention of potassium depletion when the dietary intake is inadequate in the following conditions: Patients receiving digitalis and diuretics for congestive heart failure, hepatic cirrhosis with ascites, states of aldosterone excess with normal renal function, potassium-losing nephropathy, and with certain diarrheal states.
3. The use of potassium salts in patients receiving diuretics for uncomplicated essential hypertension is often unnecessary when such patients have a normal dietary pattern. Serum potassium should be checked periodically, however, and if hypokalemia occurs, dietary supplementation with potassium-containing foods may be adequate to control milder cases. In more severe cases supplementation with potassium salts may be indicated.

CONTRAINDICATIONS: Potassium supplements are contraindicated in patients with hyperkalemia since a further increase in serum potassium concentration in such patients can produce cardiac arrest. Hyperkalemia may complicate any of the following conditions: Chronic renal failure, systemic acidosis such as diabetic acidosis, acute dehydration, extensive tissue breakdown as in severe burns, adrenal insufficiency, or the administration of a potassium-sparing diuretic (e.g., spironolactone, triamterene).

Wax-matrix potassium chloride preparations have produced esophageal ulceration in certain cardiac patients with esophageal compression due to enlarged left atrium.

All solid dosage forms of potassium chloride supplements are contraindicated in any patient in whom there is cause for arrest or delay in tablet passage through the gastrointestinal tract. In these instances, potassium supplementation should be with a liquid preparation.

WARNINGS. Hyperkalemia—In patients with impaired mechanisms for excreting potassium, the administration of potassium salts can produce hyperkalemia and cardiac arrest. This occurs most commonly in patients given potassium by the intravenous route but may also occur in patients given potassium orally. Potentially fatal hyperkalemia can develop rapidly and be asymptomatic. The use of potassium salts in patients with chronic renal disease, or any other condition which impairs potassium excretion, requires particularly careful monitoring of the serum potassium concentration and appropriate dosage adjustment.

Interaction with Potassium Sparing Diuretics—Hypokalemia should not be treated by the concomitant administration of potassium salts and a potassium-sparing diuretic (e.g., spironolactone or triamterene) since the simultaneous administration of these agents can produce severe hyperkalemia.

Gastrointestinal Lesions—Potassium chloride tablets have produced stenotic and/or ulcerative lesions of the small bowel and deaths. These lesions are caused by a high localized concentration of potassium ion in the region of a rapidly dissolving tablet, which injures the bowel wall and thereby produces obstruction, hemorrhage or perforation.

K-DUR tablets contain micro-crystalloids which disperse upon disintegration of the tablet. These micro-crystalloids are formulated to provide a controlled release of potassium chloride. The dispersibility of the micro-crystalloids and the controlled release of ions from them are intended to minimize the possibility of a high local concentration near the gastrointestinal mucosa and the ability of the KCl to cause stenosis or ulceration. Other means of accomplishing this (e.g., incorporation of potassium chloride into a wax matrix) have reduced the frequency of such lesions to less than one per 100,000 patient years (compared to 40–50 per 100,000 patient years with enteric-coated potassium chloride) but have not eliminated them. The frequency of GI lesions with K-DUR tablets is, at present, unknown. K-DUR tablets should be discontinued immediately and the possibility of bowel obstruction or perforation considered if severe vomiting, abdominal pain, distention, or gastrointestinal bleeding occurs.

Metabolic Acidosis—Hypokalemia in patients with metabolic acidosis should be treated with an alkalinizing potassium salt such as potassium bicarbonate, potassium citrate, potassium acetate, or potassium gluconate.

PRECAUTIONS: The diagnosis of potassium depletion is ordinarily made by demonstrating hypokalemia in a patient with a clinical history suggesting some cause for potassium depletion. In interpreting the serum potassium level, the physician should bear in mind that acute alkalosis per se can produce hypokalemia in the absence of a deficit in total body potassium while acute acidosis per se can increase the serum potassium concentration into the normal range even in the presence of a reduced total body potassium. The treatment of potassium depletion, particularly in the presence of cardiac disease, renal disease, or acidosis requires careful attention to acid-base balance and appropriate monitoring of serum electrolytes, the electrocardiogram, and the clinical status of the patient.

Laboratory Tests: Regular serum potassium determinations are recommended. In addition, during the treatment of potassium depletion, careful attention should be paid to acid-base balance, other serum electrolyte levels, the electrocardiogram, and the clinical status of the patient, particularly in the presence of cardiac disease, renal disease, or acidosis.

Drug Interactions: Potassium-sparing diuretics; see **WARNINGS.**

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term carcinogenicity studies in animals have not been performed.

Pregnancy Category C: Animal reproduction studies have not been conducted with K-DUR. It is also not known whether K-DUR can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. K-DUR should be given to a pregnant woman only if clearly needed.

Nursing Mothers: The normal potassium ion content of human milk is about 13 mEq per liter. Since oral potassium becomes part of the body potassium pool, so long as body potassium is not excessive, the contribution of potassium chloride supplementation should have little or no effect on the level in human milk.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: One of the most severe adverse effects is hyperkalemia (see **CONTRAINDICATIONS, WARNINGS,** and **OVERDOSAGE**). There have also been reports of upper and lower gastrointestinal conditions including obstruction, bleeding, ulceration, and perforation (see **CONTRAINDICATIONS** and **WARNINGS**); other factors known to be associated with such conditions were present in many of these patients.

The most common adverse reactions to oral potassium salts are nausea, vomiting, abdominal discomfort, and diarrhea. These symptoms are due to irritation of the gastrointestinal tract and are best managed by taking the dose with meals or reducing the dose.

Skin rash has been reported rarely.

OVERDOSAGE: The administration of oral potassium salts to persons with normal excretory mechanisms for potassium rarely causes serious hyperkalemia. However, if excretory mechanisms are impaired or if potassium is administered too rapidly intravenously, potentially fatal hyperkalemia can result (see **CONTRAINDICATIONS** and **WARNINGS**). It is important to recognize that hyperkalemia is usually asymptomatic and may be manifested only by an increased serum potassium concentration and characteristic electrocardiographic changes (peaking of T-waves, loss of P-waves, depression of S-T segment, and prolongation of the QT-interval). Late manifestations include muscle-paralysis and cardiovascular collapse from cardiac arrest.

Treatment measures for hyperkalemia include the following:

1. Elimination of foods and medications containing potassium and of potassium-sparing diuretics.
2. Intravenous administration of 300 to 500 ml/hr of 10% dextrose solution containing 10–20 units of insulin per 1,000 ml.
3. Correction of acidosis, if present, with intravenous sodium bicarbonate.
4. Use of exchange resins, hemodialysis, or peritoneal dialysis.

In treating hyperkalemia, it should be recalled that in patients who have been stabilized on digitalis, too rapid a lowering of the serum potassium concentration can produce digitalis toxicity.

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(Continued from Page 731)

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* * *

August 13-15—**Retrieved Implants and Biomaterials** (Sponsor: UUMC). Fri-Sun. Contact: Rosalie Lammle, (801) 581-8664.

September 22-24—**Central Association of Obstetricians & Gynecologists** (Sponsor: UUMC). Thurs-Sat. 10.5 hrs. Salt Lake City Marriott. Contact: (801) 333-0988.

SPONSORS OF COURSES—ABBREVIATIONS

AHA:	American Heart Association, Utah Affiliate, 645 E 400 South, Salt Lake City 84102. (801) 322-5601.
BYUHS:	Brigham Young University Health Services, McDonald Student Health Center, Brigham Young University, Provo 84602. (801) 378-2771.
CH:	Castleview Hospital (formerly Carbon Hospital), RFD 2, Box 46, Price 84501. (801) 637-4800.
CWH:	Cottonwood Hospital, 5770 S 300 East, Salt Lake City 84101. (801) 262-3461.
DMC:	Dixie Medical Center, 544 S 400 East, St George 84770. (801) 673-9681.
HCH:	Holy Cross Hospital, 1045 E First South, Salt Lake City 84102. (801) 350-4744.
ITS:	Intermountain Thoracic Society, 1616 S 11th East, Salt Lake City 84105. (801) 484-4456.
LDSH:	LDS Hospital, 8th Ave and "C" St, Salt Lake City 84143. (801) 321-1100.
LRH:	Logan Regional Hospital, 1400 N 5th East, Logan 84321. (801) 752-2050.
MDH:	McKay-Dee Hospital Center, 3939 Harrison Blvd, Ogden 84409. (801) 399-4141.
MVH:	Mountain View Hospital, 1000 E Highway 6, Payson 84651. (801) 465-9201.
144:	144th Evacuation Hospital, PO Box 8000, Salt Lake City 84108. (801) 524-3924.
OSS:	Ogden Surgical Society, PO Box 9311, Ogden 84409.
PCMC:	Primary Children's Medical Center, 320 12th Ave, Salt Lake City 84103. (801) 363-1221.
PVH:	Pioneer Valley Hospital, 3460 S 4155 West, West Valley City 84120. (801) 968-9061.
SMH:	St Mark's Hospital, 1200 E 3900 South, Salt Lake City 84117. (801) 268-7111.
UOS:	Utah Ophthalmological Society, 540 E 500 South, Salt Lake City 84102. (801) 355-7477.
USH:	Utah State Hospital, PO Box 270, Provo 84603-0270. (801) 373-4400.
UUMC:	University of Utah Medical Center, 50 N Medical Dr, Salt Lake City 84132. (801) 581-2258.
UVRMC:	Utah Valley Regional Medical Center, 1034 N Fifth West, Provo 84604. (801) 373-7850.
VAMC:	Veterans Administration Medical Center, 500 Foothill Dr, Salt Lake City 84148. (801) 582-1565.
VVMC:	Valley View Medical Center, 595 S 75 East, Cedar City 84720. (801) 586-6587.

WASHINGTON

This listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. To list Category 1 programs here please send information at least two months in advance to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 900, Seattle, WA 98121; or phone (206) 441-WSMA.

Brochures and registration forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

June 17-18—**Renal Disorders: Medical and Surgical Aspects.** Seattle. Fri-Sat. Contact: U/W, Maria Lilja, (206) 543-1050.

June 20-24—**Pathology of Lung Cancer.** Seattle. Mon-Fri. Contact: VMMC.

July 21-23—**Common Office Procedures.** Seattle. Thurs-Sat. Contact: U/W, Maria Lilja, (206) 543-1050.

(Continued on Page 734)

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Psychiatry	$ 5,100	$ 2,365	54%	$ 3,789	$ 2,052	46%
Pediatrics	7,357	2,365	68%	6,208	2,052	67%
Urology	18,571	13,735	26%	14,560	11,776	19%
Anesthesiology	19,704	13,735	30%	16,299	11,776	28%
General Surgery	30,841	17,853	42%	22,388	15,306	32%
Plastic Surgery	31,557	17,853	43%	22,961	15,306	33%
Orthopedic Surgery w/Spinal	39,744	21,971	45%	34,184	18,837	45%
Obstetrics/ Gynecology	49,812	21,971	56%	40,220	18,837	53%

* Insurance company composite rates are averages based upon 4/1/88 rates of The Doctors' Company, 6/1/87 rates of MIEC, 1988 rates of Norcal and SCPIE. Details of source data on request. No costs shown here for San Diego or Imperial County. Other surcharges, credits, reductions may apply. All costs based on mature rate (including retroactive coverage).

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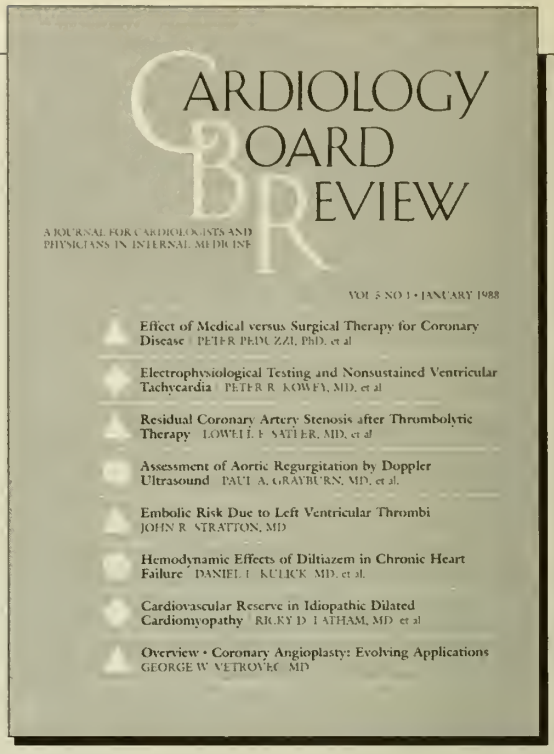

*Journals reviewed include: *Circulation, American Heart Journal, Journal of the American College of Cardiology, British Heart Journal, Chest, The American Journal of Cardiology, The New England Journal of Medicine, Annals of Internal Medicine, American Journal of Medicine*, and *The Journal of the American Medical Association*.

CONTINUING MEDICAL EDUCATION

(Continued from Page 732)

July 22-24—**First International Symposium on Pediatric Pain.** Seattle. Fri-Sun. Contact: U/W, Maria Lilja, (206) 543-1050.

July 24-29—**Psychiatry for Primary Care.** Seattle. Sun-Fri. Contact: U/W, Maria Lilja, (206) 543-1050.

July 29-31—**Seafair Anesthesia X.** Seattle. Fri-Sun. Contact: VMMC.

August 1-5—**Postgraduate Seminar in Psychology: Modern Approaches to Psychological Interviewing.** Ellensburg. Mon-Fri. Contact: Central Washington University, (509) 963-2381.

August 5—**Otology Update.** Seattle. Fri. Contact: VMMC.

August 8-14—**Summer Seminar in Medical Ethics and History.** Seattle. Mon-Sun. Contact: U/W, Maria Lilja, (206) 543-1050.

August 11-12—**Surviving the Elements.** Seattle. Thurs-Fri. Contact: U/W, Maria Lilja, (206) 543-1050.

August 29—**NW Regional Perinatal Conference: Current Issues in OB/GYN, Neonatology and Pediatrics.** Coeur d'Alene, Idaho. Thurs. Contact: (509) 624-3182.

August 31-September 3—**Second International Forum of Otorhinolaryngology.** Seattle. Wed-Sat. Contact: U/W, Maria Lilja, (206) 543-1050.

COURSE SPONSORS AND CONTACT INFORMATION

CME HARBORVIEW—Contact: Gayle Splater, Cytology Continuing Education, Dept. of Pathology, Harborview Medical Center, 325 Ninth Avenue, Seattle, WA 98104. (206) 223-5953.

CME PIERCE COUNTY—Contact: Mrs Maxine Bailey, Executive Director, College of Medical Education, 705 South Ninth, No. 203, Tacoma, WA 98405. (206) 627-7137.

U/W (UNIVERSITY OF WASHINGTON)—Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

WSMA—Washington State Medical Association, Continuing Medical Education, 2033 Sixth Ave, Suite 900, Seattle, WA 98121. (206) 441-9762.

VMMC (VIRGINIA MASON MEDICAL CENTER)—Contact: Linda Orgel, Division of Continuing Medical Education, Virginia Mason Medical Center, PO Box 900, Seattle, WA 98111. (206) 223-6898.

September 9—**Update on Anxiety and Depression.** Seattle. Fri. Contact: U/W, Maria Lilja, (206) 543-1050.

September 12-16—**16th Annual Family Practice Review Course.** Seattle. Mon-Fri. Contact: U/W, Maria Lilja, (206) 543-1050.

September 17-24—**Effective Management of Common Sports Injuries.** San Juan Islands. Sat-Sat. Contact: Kathy Rairigh, EPIC Expeditions, (208) 788-4995.

September 22-24—**Orthopedic Biomechanics.** Seattle. Thurs-Sat. Contact: VMMC.

WYOMING

June 23-26—**Wyoming Medical Society Annual Meeting.** Jackson Lake Lodge, Moran. Thurs-Sun. Contact: WMS, PO Drawer 4009, Cheyenne 82003-4009. (307) 635-2424.

July 16-23—**The Treatment of Infectious Diseases.** University of Arizona College of Medicine, Department of Family and Community Medicine, and Epic Expeditions at Yellowstone. 24 hrs. Contact: Kathy Rairigh, EPIC Expeditions, PO Box 209, Sun Valley, ID 83353. (208) 788-4995.

July 18-22—**6th Annual Update in Clinical Microbiology and Immunology.** University of Utah Medical Center at Jackson Hole. Mon-Fri. 25 hrs. Contact: UUMC, 50 N Medical Dr, Salt Lake City, UT 84132. (801) 581-2258.

July 23-30—**Up-to-date Pulmonary and Cardiac Medicine.** University of Arizona College of Medicine, Department of Family and Community Medicine, and Epic Expeditions at Jackson Hole and Yellowstone. 24 hrs. Contact: Kathy Rairigh, EPIC Expeditions, PO Box 209, Sun Valley, ID 83353. (208) 788-4995. ◆

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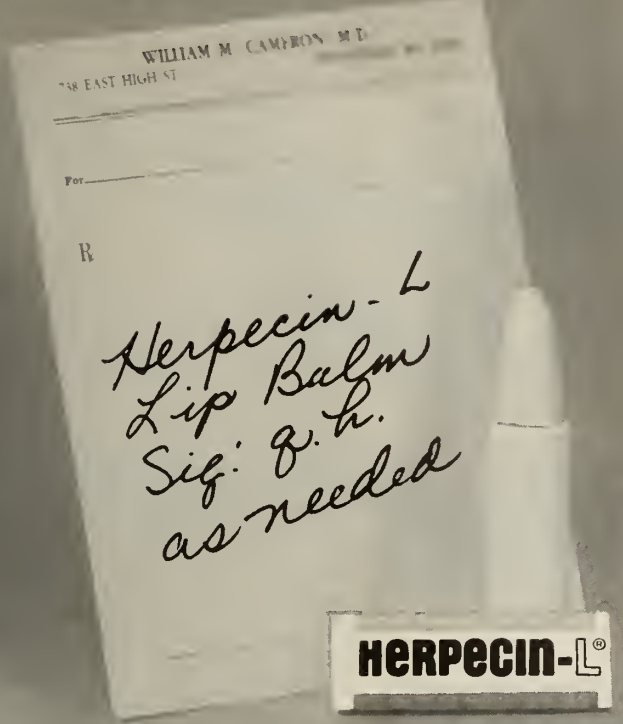

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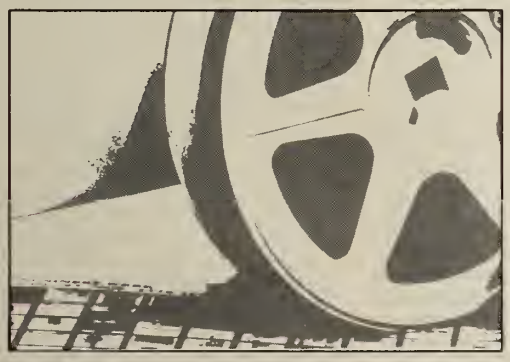

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NEAR STANFORD. Six Internists, all subspecialty trained and members of clinical faculty at Stanford, interested in an Associate with subspecialty interest and training. Should be well grounded in Internal Medicine. Send CV to Dr Bigler, El Camino Internal Medical Group, 125 South Dr, Mountain View, CA 94040.

CRESCENT CITY, CALIFORNIA. Exciting position available at a growing 24,000 visit ER in a rural, coastal community. Fee-for-service with possibility of six figure income. Send CV to Art B. Wong, MD, FACEP, 1 Maritime Plaza, Ste 710, San Francisco, CA 94111.

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ARIZONA-BASED PHYSICIAN recruiting firm has opportunities coast-to-coast. "Quality Physicians for Quality Clients since 1972." Call (602) 990-8080; or send CV to Mitchell & Associates, Inc, PO Box 1804, Scottsdale, AZ 85252.

DERMATOLOGIST. Visalia Medical Clinic has an opening for a BC/BE Dermatologist now staffed by one physician who has been with the Clinic for 15 years. Located in the San Joaquin Valley in central California and population approximately 350,000. Progressive city of 62,000, near national parks and the ocean. Compensation is incentive oriented with advancement to full partnership after one year. Excellent fringe benefits. If interested, CV to John G. Heinsohn, Administrator, 5400 W. Hillsdale, Visalia, CA 93291; (209) 733-5222.

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PEDIATRICIAN position available with multispecialty group; BE/BC required; strong incentive plan; benefits included; retirement program and located in San Luis Obispo, California on the central coast. Send CV to Administration/Recruitment, San Luis Medical Clinic, 1235 Osos St, San Luis Obispo, CA 93401.

OBSTETRICIAN/GYNECOLOGIST position available with multispecialty group; BE/BC required; strong incentive plan; benefits included; retirement program and located in San Luis Obispo, California on the central coast. Send CV to Administration/Recruitment, San Luis Medical Clinic, 1235 Osos St, San Luis Obispo, CA 93401.

INTERNIST with interest in trauma, Cardiology, or Gastroenterology, also willing to practice general Internal Medicine in a prosperous family-oriented community in southeastern New Mexico. Please submit CV to Rita Longino, Southwest Community Health Services, PO Box 26666, Albuquerque, NM 87125-6666; or call 1 (800) 545-4030, ext 8300.

FAMILY PHYSICIANS sought to join established physicians or develop solo practices in prosperous communities in New Mexico and Colorado. Please submit CV to Rita Longino, Southwest Community Health Services, PO Box 26666, Albuquerque, NM 87125-6666; or call 1 (800) 545-4030, ext 8300.

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PRIMARY CARE, INTERNIST, OR FAMILY PRACTITIONER who is BC/BE for satellite clinic in a rural community 30 minutes from main clinic, which is a 35 physician multispecialty group. Guaranteed income plus excellent benefits. No investment required. Send CV to Search Committee, Walla Walla Clinic, 55 W. Tietan, Walla Walla, WA 99362.

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(Continued on Page 738)

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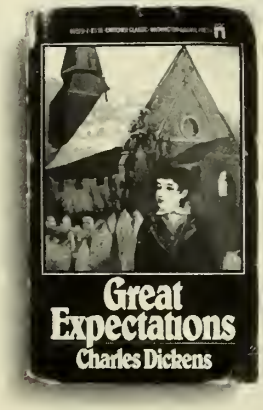

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(Continued from Page 736)

PHYSICIANS WANTED

CARDIOLOGIST, NON-INVASIVE, BC/BE to join six physician group in the Portland metropolitan area—one Cardiologist, one Hematologist/Oncologist, two Gastroenterologists, two Internists. Send CV to Hudson's Bay Medical Group, Inc, PS, 2102 E. McLoughlin Blvd, Vancouver, WA 98661; (206) 695-1334.

CALIFORNIA, SAN FRANCISCO BAY AREA. Full-time career Emergency Physician wanted for high volume Emergency Department. Emergency Medicine Board certified or Board-ready mandatory to participate in a group of twenty full-time staff physicians seeing over 300 patients per day. Salaried position, excellent benefits include three weeks paid vacation, one week CME, paid malpractice, health and life insurance, corporate shareholdership in three years. Send CV or contact David Gallagher, MD, 27400 Hesperian Blvd, Hayward, CA 94545.

INTERNIST, BC/BE to join six physician group in Portland metropolitan area—one Cardiologist, one Hematologist/Oncologist, two Gastroenterologists, two Internists. Send CV to Hudson's Bay Medical Group, Inc, PS, 2102 E. McLoughlin Blvd, Vancouver, WA 98661; (206) 695-1334.

CALIFORNIA. BE/BC Internist to join staff of eight Internists in 14 physician multispecialty group located in central San Joaquin Valley. Competitive starting salary and full benefits. Excellent living and practice environment. Send CV to Frank Kelley, MD, Kaweah Medical Group, 222 W. Willow, Visalia, CA 93291.

UROLOGIST BC/BE. To be second Urologist in a 35 physician multispecialty clinic. Guaranteed salary and immediate full participation in incentive program. Excellent benefit package and excellent recreational, cultural, and educational opportunities. Send CV to Search Committee, 55 W. Tietan, Walla Walla, WA 99362.

FAMILY PRACTICE/GENERAL PRACTICE wanted for full-time practice to work three days a week and share with another Practitioner. Rural setting, good pay, nice people. Can commute for two nights a week, one hour Sacramento, one hour and 15 minutes Nevada City, two hours San Francisco. Contact Charles Rath, MD, 199 E. Webster St, Colusa, CA 95932; (916) 458-7739.

GASTROENTEROLOGIST position available with multispecialty group; BE/BC required; strong incentive plan; benefits included; retirement program and located in San Luis Obispo, California on the central coast. Send CV to Administration/Recruitment, San Luis Medical Clinic, 1235 Osos St, San Luis Obispo, CA 93401.

FAMILY PRACTITIONER position available with multispecialty group; BE/BC required; strong incentive plan; benefits included; retirement program and located in San Luis Obispo, California on the central coast. Send CV to Administration/Recruitment, San Luis Medical Clinic, 1235 Osos St, San Luis Obispo, CA 93401.

EUGENE, OREGON. Well-established, eight physician Family Practice group is seeking BC/BE Family Physician with interest in OB. Anticipate partnership after one year. Exceptional cultural and recreational opportunities. Home of the University of Oregon. Please send CV to Rob Daugherty, MD, River Road Medical Group, 2400 River Rd, Eugene, OR 97404; or call (503) 688-7527.

WASHINGTON. Full-time Emergency Physician needed for moderate volume ED in Yakima area. $100,000 possible plus partial malpractice coverage. Near mountains, skiing, etc. Two and one-half hours from Seattle. Send CV to Ted Palmatier, MD, FACEP, 110 S. Ninth Ave, Yakima, WA 98902; or call (509) 575-5060.

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GENERAL INTERNIST position available with multispecialty group; BE/BC required; strong incentive plan; benefits included; retirement program and located in San Luis Obispo, California on the central coast. Send CV to Administration/Recruitment, San Luis Medical Clinic, 1235 Osos St, San Luis Obispo, CA 93401.

PEDIATRICIAN—SUNNY SOUTHERN CALIFORNIA. Rapidly growing, family oriented community at the foot of the mountains near Palm Springs needs another Pediatrician. Beautiful hospital expanding its services will provide financial guarantee for the right BE/BC physician. For more information and a personal interview, please call Jeffrey Gowan at (800) 288-1210 and/or send your CV to Merritt, Hawkins & Associates, 500 N. Newport Blvd, Ste 204, Newport Beach, CA 92663.

INTERNIST, BC/BE, to join two member primary care clinic, suburb, Seattle, Washington. Spacious, new office near top rate hospital. Send letter of career goals, interests, and CV to Number 100, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

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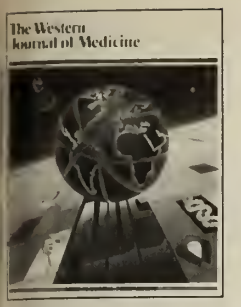
ONCOLOGIST/INTERNIST BC/BE wanted to join hospital-based multispecialty clinic near San Francisco. Complete benefit package. Send résumé to Gary Hillman, MD, Chief, Department of Medicine, Permanente Medical Group, 1150 Veterans Blvd, Redwood City, CA 94063; or call (415) 780-2626.

(Continued on Page 740)

SPECIAL ISSUES



AIDS—A Global Perspective

The short and remarkable history of AIDS epidemiology began in 1981 with the description of the clinical syndrome in California and New York. In the 6 years that have followed, intensive epidemiologic studies have defined the mode of spread of AIDS and laid the foundation for current control efforts. Serosurveys and retrospective clinical studies have been used to trace the temporal origins of the pandemic prior to 1981, while prospective studies and an increasingly comprehensive worldwide surveillance system have provided more accurate data for the years following 1981. AIDS cases have now been reported and investigated throughout the world.

This issue, from the Special Programme on AIDS of the World Health Organization, considers the methods and limitations of AIDS case reporting and HIV serologic studies, summarizes modes of HIV transmission, defines geographic patterns of spread, and examines the epidemiology of HIV infections by continent.

—Jonathan M. Mann, MD
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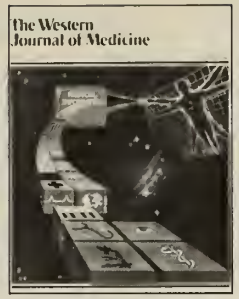

Medical Informatics

I would suggest that the computer in its relation to medicine is analogous to that of the microscope in the last century. . . . The analogous role that I believe the computer is now taking on is also that of a breakthrough tool—one enabling us to explore and better understand the informational and cognitive foundations of medicine. Its application to the classification and retrieval of data and to the management of information will result in a deeper insight into the structure of medical information and knowledge itself.

—Marsden S. Blois, PhD, MD

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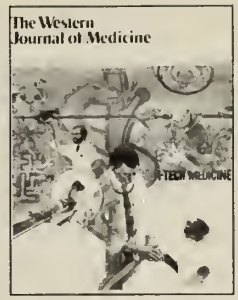

High-Tech Medicine

Progress in medical science seems to come in rushes. There are long periods of time during which we mainly fine-tune the status quo: third-generation drugs, better optics for endoscopes, more accurate assays, rapid development of x-ray film and so forth. Then, out of nowhere, a surge of new discoveries whose potential applications to medical practice seem limitless takes our breath away. We are now in such an epoch. Powerful and precise lasers. Almost unbelievable organ transplantation. Complex and uniquely informative magnetic resonance imaging and positron emission tomography. Exquisitely specific monoclonal antibodies. And the immense potential of modern molecular biology. This rush of new advances, collapsed into such a brief period of time, boggles the mind.

—R. Paul Robertson, MD

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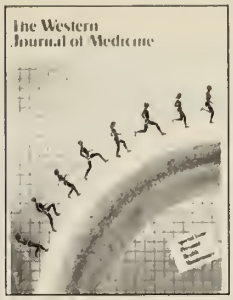

Personal Health Maintenance

The goal of this special issue is to provide an authoritative, current guide to disease prevention and health promotion. The contributors are distinguished experts in public health, epidemiology and clinical medicine.

—John H. Holbrook, MD

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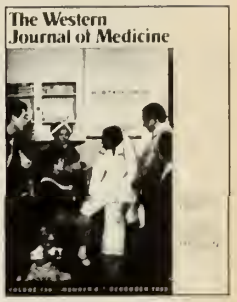

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Reprinted as a book because of extraordinary demand

The barriers may be great indeed when an American-trained physician undertakes to treat a patient from another ethnic or religious background. Too little attention has been given to developing better or even adequate communication across all these different cultures. The subject is of worldwide social, economic and political importance, and on a more individual and personal basis it is important in patient care.

—Malcolm S.M. Watts, MD

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(Continued from Page 738)

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GENERAL SURGEON. Opportunity for BC/BE Surgeon with fellowship or experience in Vascular Surgery to join Surgeon in active practice in southeastern Washington state; well-equipped 71-bed hospital undergoing expansion. Send current CV to J. Griffith, PO Box 6128, Kennewick, WA 99336.

PHYSICIAN OPENING. Ambulatory care/minor emergency center. Full/part-time for Family Practice/Internal Medicine/Emergency Medicine trained, experienced physician located in Tacoma area. Flexible scheduling, pleasant setting, quality medicine. Contact David R. Kennel, MD, 5900 100th St Southwest, Ste 31, Tacoma, WA 98499; (206) 584-3023 or 582-2542.

OB/GYN—IDAHO-SUN VALLEY. Skiing is one of the benefits of having your practice in this recreation-rich area. Hospital is expanding its OB/GYN services and needs one to two BE/BC hard-working OB/GYNs to service this area. Big practice. Support of excellent, quality medical staff. For more information call Jeffrey Gowan at (800) 288-1210 and/or send CV to 500 N. Newport Blvd, Ste 204, Newport Beach, CA 92663.

INTERNIST, BC/BE, California license. Women's care clinic. Duties will include admissions and inpatient care. Send résumé to Dr Susann J. Steinberg, Medical Director, Access Health Care, 26 California St, San Francisco, CA 94111.

FAMILY PRACTICE—IDAHO-SUN VALLEY. Skiing is one of the great amenities of living and practicing in this recreation-rich area. If you desire to practice in association with young BC Family Practitioners who do OB in a nice family-oriented community and are supportive of another new physician, if you wish to make an above-average living, if you would like to have an option of practice management provided for you, please call Jeffrey Gowan at (800) 288-1210 and/or send CV to 500 N. Newport Blvd, Ste 204, Newport Beach, CA 92663 for additional details and a personal interview.

PHYSICIANS WANTED

FAMILY PRACTICE—SUNNY SOUTHERN CALIFORNIA. Rapidly growing, family oriented community at the foot of the mountains near Palm Springs needs another Family Practitioner. Beautiful hospital expanding its services will provide financial guarantee for the right BE/BC physician. For more information and a personal interview, please call Jeffrey Gowan at (800) 288-1210 and/or send your CV to Merritt, Hawkins & Associates, 500 N. Newport Blvd, Ste 204, Newport Beach, CA 92663.

WASHINGTON. Excellent opportunity for caring BC/BE physician to join a 35 member multispecialty clinic as the second physician in our expanding facility based Immediate Care Department. Competitive salary and generous fringe benefits including paid education leave, vacation, insurance, and retirement. Send inquiries and CV to R. G. Caudill, MD, Walla Walla Clinic, 55 W. Tietan, Walla Walla, WA 99362.

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PHYSICIANS WANTED. We have full and part-time locum tenens opportunities available with guaranteed incomes and paid malpractice. For more information, contact John Smith, Locum Tenens, Inc (A Division of Jackson and Coker), 400 Perimeter Center Terrace, Ste 760 WJM, Atlanta, GA 30346; 1 (800) 544-1987.

GENERAL INTERNIST needed for large hospital-based multispecialty clinic. University associated residency program. Attractive salary and complete benefit package. Pleasant setting. BC/BE. California license required. Contact Dennis L. Ostrem, MD, Chief Internal Medicine, The Permanente Medical Group, Inc, PO Box 254999, Sacramento, CA 95865-4999 or call (916) 973-5781. An Equal Opportunity Employer.

FAMILY PRACTITIONER. Busy four physician Family Practice group (including OB) seeks replacement for partner departing fall, 1988. Located in Alaska's capital city in the Tongass National Forest offering year 'round recreation including skiing, boating, and hiking. Guaranteed salary with excellent fringe benefits and opportunity for partnership within one year. Send CV to Sarah A. Isto, MD, Valley Medical Care, Inc, 9309 Glacier Hwy, B-301, Juneau, AK 99801; (907) 789-3181.

PEDIATRICIAN, BE/BC, needed July 1988 in four-season playground. Excellent practice opportunity with positive financial success. Send CV to Dr Gerald E. Carlson, Women's Medical Clinic, 1203 10th St South, Nampa, ID 83651; (208) 467-2400.

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OB/GYN, SEATTLE AREA. Rapidly growing practice seeks third OB/GYN. Come practice in a picturesque community on Puget Sound. Nearby mountains and lakes provide limitless recreational opportunities. University of Washington continuing education minutes away. For excellent incentive-oriented compensation and benefits contact Philip DuBois, MD, 7935 216th St SW, Ste E, Edmonds, WA 98020; (206) 775-0681.

FAMILY PRACTITIONER or GENERAL PRACTITIONER—BC/BE. For Family Practice in a large central California community and migrant health clinic located in the central San Joaquin Valley serving large Hispanic and Southeast Asian medically underserved population. Competitive salary with excellent fringe benefits and paid malpractice. Send CV and inquiries to Director, Sequoia Community Health Foundation, Inc, 2790 S. Elm Ave, Fresno, CA 93706.

PHYSICIAN WANTED. Family Practice Physician to join 16 physician multispecialty group with attached 40-bed hospital located in southern Idaho. Contact Business Administrator, Box 1233, Twin Falls, ID 83301.

MONTEREY PENINSULA, CALIFORNIA. BC/BE General Internist to join four other Internists now in multispecialty group. Guaranteed income arrangement leading to partnership. Busy, well established clinic practice. Excellent office, lab, x-ray equipment. Outstanding community hospital. Submit CV, availability date to Robert H. Cleland, MD, Central Medical Group, 505 Central Ave, Pacific Grove, CA 93950.

ENJOY COUNTRY LIVING and outstanding year 'round outdoor recreation, excellent school system, clean environment! Join two BC Internists with growing practice in historical Wyoming community. We seek BE/BC Internist candidates recently trained or in university affiliated program. Income guarantee, paid malpractice and health insurance, more! Contact Cynthia Lacro, PRO-SEARCH, 305 NE 102nd Ave, Portland, OR 97220; 1 (800) 237-6906.

INTERNIST—SUNNY SOUTHERN CALIFORNIA. Rapidly growing, family oriented community at the foot of the mountains near Palm Springs needs another Internist. Beautiful hospital expanding its services will provide financial guarantee for the right BE/BC physician. For more information and a personal interview, please call Jeffrey Gowan at (800) 288-1210 and/or send your CV to Merritt, Hawkins & Associates, 500 N. Newport Blvd, Ste 204, Newport Beach, CA 92663.

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(Continued on Page 742)

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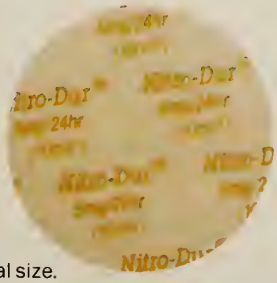

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BRIEF SUMMARY

INDICATIONS AND USAGE: This drug product has been conditionally approved by the FDA for the prevention and treatment of angina pectoris due to coronary artery disease. The conditional approval reflects a determination that the drug may be marketed while further investigation of its effectiveness is undertaken. A final evaluation of the effectiveness of the product will be announced by the FDA.

CONTRAINDICATIONS: Intolerance of organic nitrate drugs, marked anemia.

WARNINGS: The NITRO-DUR system should be used under careful clinical and/or hemodynamic monitoring in patients with acute myocardial infarction or congestive heart failure.

In terminating treatment of anginal patients, both the dosage and frequency of application must be gradually reduced over a period of 4 to 6 weeks in order to prevent sudden withdrawal reactions, which are characteristic of all vasodilators in the nitroglycerin class.

PRECAUTIONS: Symptoms of hypotension, such as faintness, weakness or dizziness, particularly orthostatic hypotension, may be due to overdosage. If during the course of treatment these symptoms occur, the dosage should be reduced or use of the product discontinued.

NITRO-DUR is not intended for use in the treatment of acute anginal attacks. For this purpose, occasional use of sublingual nitroglycerin may be necessary.

Pregnancy: Pregnancy Category C. Animal reproduction studies have not been conducted with NITRO-DUR. It is also not known whether nitroglycerin can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Nitroglycerin should be given to a pregnant woman only if clearly needed.

Nursing Mothers: It is not known whether nitroglycerin is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when NITRO-DUR is administered to a nursing woman.

ADVERSE REACTIONS: Transient headache is the most common side effect, especially when higher doses of the drug are administered. Headaches should be treated with mild analgesics while continuing NITRO-DUR therapy. If headache persists, the NITRO-DUR dosage should be reduced or use of the product discontinued.

Adverse reactions reported less frequently include hypotension, increased heart rate, faintness, flushing, dizziness, nausea, vomiting, and dermatitis. Except for dermatitis, these symptoms are attributed to the pharmacologic effects of nitroglycerin. However, they may be symptoms of overdosage. When they persist, the NITRO-DUR dosage should be reduced or use of the product discontinued.

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(Continued from Page 740)

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MONTANA. BC Family Practitioner seeks partner with interests in Obstetrics and Rural Medicine to join busy practice in southeast Montana. Office on hospital/NH campus. First year income guarantee, relocation assistance, and other benefits. Enjoy comforts of friendly small community living and recreation that only Montana can offer! Send CV to Cynthia Lacro, PRO-SEARCH, 305 NE 102nd Ave, Portland, OR 97220; (800) 237-6906.

WASHINGTON. Openings for career oriented Emergency Physicians, BC/BE in Emergency or Primary medical specialty. In a Seattle metropolitan hospital with 35,000 annual visits. Excellent salary with partnership potential in stable, growing group. Contact Beth Welsh at Valley Medical Center, 400 S. 43rd St, Renton, WA 98055.

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PORTLAND, OREGON. Established, rapidly growing practice seeks BE/BC Internist. Multispecialty group active in private and HMO practice with satellite office. Salary and benefits first two years lead to partnership. Send CV to SMC, 10535 NE Glisan St, Portland, OR 97220, Attn: Dick Hamilton; (503) 256-0594.

FAMILY PRACTICE, PUGET SOUND. 23 physician multispecialty group is seeking Family Practitioner. Our facility has in-house lab and x-ray facilities and is conveniently located one block from Level III hospital. Attractive salary and benefits; partnership opportunity. Send CV to Carol Larsen, Acting Director, c/o The Western Clinic, PO Box 5467, Tacoma, WA 98405.

RHEUMATOLOGIST. Immediate opening for BC/BE Rheumatologist with large prepaid group practice in San Francisco bay area. Busy clinical practice with opportunities for teaching and research. University appointment possible. Competitive salary. Generous benefit package. Respond with CV to Joseph Mason, MD, Chief, Department of Medicine, Permanente Medical Group, 260 International Cir, San Jose, CA 95119, or phone (408) 972-6560.

FAMILY PHYSICIAN, RESIDENCY TRAINED BC/BE. Busy three doctor Family Practice in Woodland, California seeking fourth associate. OB optional. Current doctors are clinical faculty at UC Davis. Practice includes all aspects of family medicine. Woodland is centrally located with easy access to Sacramento, Davis, San Francisco, and Lake Tahoe. Contact J. T. Barrett, MD, W. J. Blevins Medical Group, Inc., 520 Cottonwood St, Ste 4, Woodland, CA 95695.

FAMILY PRACTICE PHYSICIAN WANTED. Salt Lake area family practice clinic. Close to skiing and excellent outdoor recreational opportunities. Income guaranteed and excellent benefits. Contact Robert Davis, MD, Director, Family Medical Center, 1781 West 9000 South, West Jordan, UT 84088; (801) 562-9100.

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MAKE YOURSELF part of the rich tapestry that is New Mexico. Family Physicians needed for practice settings in southeast New Mexico, with focus on primary care. The climate is excellent, the quail hunting outstanding! BC/BE preferred. Financial incentives available. Contact NM Health Resources, PO Box 27650, Albuquerque, NM 87125; (505) 242-0633.

CALIFORNIA
Primary Care Physicians needed to work as *locum tenens* in northern California. Radiologists needed statewide. High salary, paid malpractice. Work whenever you like. Permanent placements as well.
Contact Carol Sweig, Director, (415) 673-7676. Western Physicians Registry, 710 Van Ness Ave, San Francisco, CA 94102.

SACRAMENTO. BC/BE Family Physicians needed for full-time primary care clinic, part-time ER/part-time primary care clinic, or full-time in our ER. We are a large-staff model HMO offering competitive salary, excellent benefit package, and shareholder status. California license required. Contact Richard Fury, MD, 1001 Riverside Ave, Roseville, CA 95678 or call (916) 784-4620. EOE.

CALIFORNIA. RESORT COMMUNITY servicing 25,000 people located in the San Bernardino national forest seeks Internists to join the expanding medical staff of their newer 28-bed hospital. This area is famous for picturesque lake resorts and downhill alpine skiing. Practice seeks physicians experienced in rural medicine and who desire a family oriented, mountainous community. A net income guarantee of $100,000 is offered. For more information call David King at (800) 288-1210 or send CV to 500 N. Newport Blvd, Ste 204, Newport Beach, CA 92663.

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STUDENT HEALTH SERVICE. Staff Physician is sought to provide primary care at university outpatient clinic. Ten month permanent position starting September 1. Annual salary: $52,332-$63,036. Excellent benefits. Forty hour work week. Send vitae by July 1 to Tom Beckman, California State University Chico, Chico, CA 95929.

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SAN FRANCISCO. Outstanding opportunity for BC/BE Internist, Family Practitioner, OB/GYN, or Orthopedic Surgeon at 260-bed community hospital in the dynamic South of Market area. Excellent opportunity to join busy, growing practices. Competitive salary and benefits package. Send CV to Walter Kopp, St. Luke's Hospital, 3555 Army St, San Francisco, CA 94110; (415) 641-6543.

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BC/BE GENERAL INTERNIST, or subspecialist with a strong interest in general Internal Medicine to join a partnership with two other Internists, in a challenging practice of primary care and consultation. We are located in northern California with spectacular redwood and coastal scenery. We have an excellent 50-bed hospital with five-bed ICU. Contact Richard O. Buscho, MD, 3304 Renner Dr, Fortuna, CA 95540; (707) 725-4477.

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SURGERY, CALIFORNIA. BE/BC General/Thoracic Surgeon to join staff of 14 physician multispecialty group located in the central San Joaquin Valley. Competitive starting salary and full benefits. Excellent living and practice environment. Send CV to William R. Winn, MD, Kaweah Medical Group, Inc., 222 West Willow St, Visalia, CA 93291.

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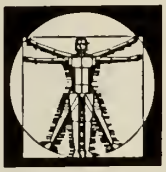

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CALIFORNIA, BERKELEY. Emergency physician group seeking physicians for full-time positions at community hospital-based urgent care center. Applicant must be at least two year post internship. Experience in primary care settings is required. Salary and work conditions are highly competitive. Contact Alta Emergency Medical Group, PO Box 1233, Berkeley, CA 94701.

NORTHERN CALIFORNIA, EMERGENCY MEDICINE. Full-time positions available in the Emergency Department at the University of California, Davis, Medical Center. The University serves a large region of northern California and is a major trauma center. Emergency physicians teach and supervise medical students and housestaff (240 per year) in addition to treating patients. Emergency Department physicians also provide medical control for UCDMC Life Flight, director of base station activities, and are actively involved in trauma care. Opportunities exist for involvement in other UCD School of Medicine teaching activities. Applicants should send CV to Robert W. Derlet, MD, Chief, Division of Emergency Medicine, University of California, Davis, Medical Center, 2315 Stockton Blvd., Sacramento, CA 95817.

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(Continued on Page 752)

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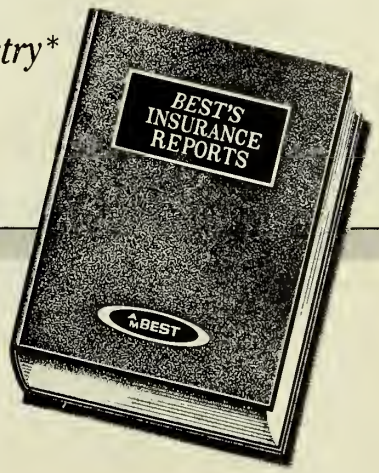

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96th ANNUAL MEETING
IDAHO MEDICAL ASSOCIATION
SUN VALLEY, IDAHO—JULY 21-23, 1988

AN INVITATION TO SUN VALLEY

We are pleased to extend to you a cordial invitation to attend the 96th Annual Meeting of the Idaho Medical Association in the beautiful setting of Idaho's Sun Valley. An excellent scientific session has been planned that should appeal to all types of physicians—family practitioners and specialists alike. It should be a good opportunity not only to enjoy beautiful Sun Valley, but also receive six credit hours of Category I at an informative scientific session.

THOMAS J. SETTER, MD, PRESIDENT
IDAHO MEDICAL ASSOCIATION

THURSDAY, JULY 21, 1988

9:00 AM-5:00 PM HOUSE OF DELEGATES
KENOTE SPEAKER
James E. Davis, MD
President, American Medical Association

SCIENTIFIC SESSION • FRIDAY, JULY 22, 1988

8:15 AM Welcome
Thomas J. Setter, MD, President, IMA

8:30-9:30 AM **EPIDEMIOLOGY AND TRANSMISSION OF HIV INFECTION**
Merle A. Sande, MD

10:00-12 Noon **LASER APPLICATIONS IN SURGERY AND MEDICINE**
Richard M. Dwyer, MD

1:30-2:30 PM **THE EMOTIONAL IMPACT OF MALPRACTICE AND ITS EFFECT ON THE PHYSICIAN AND FAMILY**
Sara C. Charles, MD

2:45-4:00 PM **PANEL DISCUSSION**
Sara C. Charles, MD

4:00-5:00 PM **DIAGNOSIS AND TREATMENT OF COMPLICATIONS OF HIV INFECTION**
Merle A. Sande, MD

SATURDAY, JULY 23

8:30 AM Closing Session, House of Delegates

Registration Fee: $150 for non-IMA members and out-of-state physicians
For Information Contact: Idaho Medical Association, P.O. Box 2668, Boise, ID 83701
Telephone: (208) 344-7888

FACULTY

Merle A. Sande, MD
Professor and Vice Chairman
Department of Medicine
University of California, San Francisco
Chief, Medical Service
San Francisco General Hospital
San Francisco, California

Richard M. Dwyer, MD
Assistant Clinical Professor of Medicine
Harbor-UCLA Medical Center
Torrance, California

Sara C. Charles, MD
Associate Professor of Clinical Psychiatry
Department of Psychiatry
University of Illinois at Chicago
Chicago, Illinois

96th ANNUAL MEETING—IDAHO MEDICAL ASSOCIATION
SUN VALLEY—JULY 21-23, 1988

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Confirmed reservations require an advance deposit equal to one night's room rental.

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Questions: Call Sun Valley toll-free Reservations: (800) 635-8261.
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IDAHO MEDICAL ASSOCIATION
SUN VALLEY, IDAHO
JULY 21-23, 1988

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HOTEL ROOMS: Sun Valley Lodge or Inn
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☐ Studio, $85 per day ☐ One-bedroom, $105 per day
☐ Two-bedroom, $130 per day ☐ Three-bedroom, $160 per day ☐ Four-bedroom, $195 per day

Each additional person: $10

Deadline for Reservations: June 21, 1988
Cancellations: No deposit refunds on cancellations received less than 7 days prior to arrival. There is a $10 per person processing charge on all cancellations.

WHEN ACID REFLUX ERUPTS

Zantac dramatically lessens pain of acid reflux[1] by inhibiting the formation of acid at its source–an action unique among pharmaceutical agents indicated for the treatment of gastroesophageal reflux disease.

Zantac® *Tablets*

ranitidine HCl/Glaxo 150 mg tablets bid

The only H_2-antagonist indicated for the treatment of gastroesophageal reflux disease

1. Sontag S, Robinson M, McCallum R, et al: Ranitidine therapy for gastroesophageal reflux disease: Results of a large double-blind trial. *Arch Intern Med* 1987; 147:1485-1491.

See next page for Brief Summary of Product Information.

Glaxo/ ROCHE

ZANTAC® 150 Tablets
(ranitidine hydrochloride)
ZANTAC® 300 Tablets
(ranitidine hydrochloride)

BRIEF SUMMARY

The following is a brief summary only. Before prescribing, see complete prescribing information in ZANTAC® product labeling.

INDICATIONS AND USAGE: ZANTAC® is indicated in:
1. Short-term treatment of **active duodenal ulcer.** Most patients heal within four weeks.
2. **Maintenance therapy** for duodenal ulcer patients at reduced dosage after healing of acute ulcers.
3. The treatment of **pathological hypersecretory conditions** (eg, Zollinger-Ellison syndrome and systemic mastocytosis).
4. Short-term treatment of **active, benign gastric ulcer.** Most patients heal within six weeks and the usefulness of further treatment has not been demonstrated.
5. Treatment of **gastroesophageal reflux disease (GERD).** Symptomatic relief commonly occurs within one or two weeks after starting therapy. Therapy for longer than six weeks has not been studied.

In active duodenal ulcer, active, benign gastric ulcer, hypersecretory states, and GERD, concomitant antacids should be given as needed for relief of pain.

CONTRAINDICATIONS: ZANTAC® is contraindicated for patients known to have hypersensitivity to the drug.

PRECAUTIONS: General: 1. Symptomatic response to ZANTAC® therapy does not preclude the presence of gastric malignancy.
2. Since ZANTAC is excreted primarily by the kidney, dosage should be adjusted in patients with impaired renal function (see **DOSAGE AND ADMINISTRATION**). Caution should be observed in patients with hepatic dysfunction since ZANTAC is metabolized in the liver.

Laboratory Tests: False-positive tests for urine protein with Multistix® may occur during ZANTAC therapy, and therefore testing with sulfosalicylic acid is recommended.

Drug Interactions: Although ZANTAC has been reported to bind weakly to cytochrome P-450 in vitro, recommended doses of the drug do not inhibit the action of the cytochrome P-450-linked oxygenase enzymes in the liver. However, there have been isolated reports of drug interactions which suggest that ZANTAC may affect the bioavailability of certain drugs by some mechanism as yet unidentified (eg, a pH-dependent effect on absorption or a change in volume of distribution).

Carcinogenesis, Mutagenesis, Impairment of Fertility: There was no indication of tumorigenic or carcinogenic effects in lifespan studies in mice and rats at doses up to 2,000 mg/kg/day.

Ranitidine was not mutagenic in standard bacterial tests (*Salmonella, E. coli*) for mutagenicity at concentrations up to the maximum recommended for these assays.

In a dominant lethal assay, a single oral dose of 1,000 mg/kg to male rats was without effect on the outcome of two matings per week for the next nine weeks.

Pregnancy: ***Teratogenic Effects: Pregnancy Category B:*** Reproduction studies have been performed in rats and rabbits at doses up to 160 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to ZANTAC. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers: ZANTAC is secreted in human milk. Caution should be exercised when ZANTAC is administered to a nursing mother.

Pediatric Use: Safety and effectiveness in children have not been established.

Use in Elderly Patients: Ulcer healing rates in elderly patients (65 to 82 years of age) were no different from those in younger age groups. The incidence rates for adverse events and laboratory abnormalities were also not different from those seen in other age groups.

ADVERSE REACTIONS: The following have been reported as events in clinical trials or in the routine management of patients treated with oral ZANTAC®. The relationship to ZANTAC therapy has been unclear in many cases. Headache, sometimes severe, seems to be related to ZANTAC administration.

Central Nervous System: Rarely, malaise, dizziness, somnolence, insomnia, and vertigo. Rare cases of reversible mental confusion, agitation, depression, and hallucinations have been reported, predominantly in severely ill elderly patients. Rare cases of reversible blurred vision suggestive of a change in accommodation have been reported.

Cardiovascular: Rare reports of tachycardia, bradycardia, and premature ventricular beats.

Gastrointestinal: Constipation, diarrhea, nausea/vomiting, and abdominal discomfort/pain.

Hepatic: In normal volunteers, SGPT values were increased to at least twice the pretreatment levels in 6 of 12 subjects receiving 100 mg qid IV for seven days, and in 4 of 24 subjects receiving 50 mg qid IV for five days. With oral administration there have been occasional reports of reversible hepatitis, hepatocellular or hepatocanalicular or mixed, with or without jaundice.

Musculoskeletal: Rare reports of arthralgias.

Hematologic: Reversible blood count changes (leukopenia, granulocytopenia, thrombocytopenia) have occurred in a few patients. Rare cases of agranulocytosis or of pancytopenia, sometimes with marrow hypoplasia, have been reported.

Endocrine: Controlled studies in animals and man have shown no stimulation of any pituitary hormone by ZANTAC (ranitidine hydrochloride) and no antiandrogenic activity, and cimetidine-induced gynecomastia and impotence in hypersecretory patients have resolved when ZANTAC has been substituted. However, occasional cases of gynecomastia, impotence, and loss of libido have been reported in male patients receiving ZANTAC, but the incidence did not differ from that in the general population.

Integumentary: Rash, including rare cases suggestive of mild erythema multiforme, and rarely, alopecia.

Other: Rare cases of hypersensitivity reactions (eg, bronchospasm, fever, rash, eosinophilia) and small increases in serum creatinine.

OVERDOSAGE: Information concerning possible overdosage and its treatment appears in the full prescribing information.

DOSAGE AND ADMINISTRATION: Active Duodenal Ulcer: The current recommended adult oral dosage is 150 mg twice daily. An alternate dosage of 300 mg once daily at bedtime can be used for patients in whom dosing convenience is important. The advantages of one treatment regimen compared to the other in a particular patient population have yet to be demonstrated.

Maintenance Therapy: The current recommended adult oral dosage is 150 mg at bedtime.

Pathological Hypersecretory Conditions (such as Zollinger-Ellison syndrome): The current recommended adult oral dosage is 150 mg twice a day. In some patients it may be necessary to administer ZANTAC® 150-mg doses more frequently. Doses should be adjusted to individual patient needs, and should continue as long as clinically indicated. Doses up to 6 g/day have been employed in patients with severe disease.

Benign Gastric Ulcer: The current recommended adult oral dosage is 150 mg twice a day.

GERD: The current recommended adult oral dosage is 150 mg twice a day.

Dosage Adjustment for Patients with Impaired Renal Function: On the basis of experience with a group of subjects with severely impaired renal function treated with ZANTAC, the recommended dosage in patients with a creatinine clearance less than 50 ml/min is 150 mg every 24 hours. Should the patient's condition require, the frequency of dosing may be increased to every 12 hours or even further with caution. Hemodialysis reduces the level of circulating ranitidine. Ideally, the dosage schedule should be adjusted so that the timing of a scheduled dose coincides with the end of hemodialysis.

HOW SUPPLIED: ZANTAC® 300 Tablets (ranitidine hydrochloride equivalent to 300 mg of ranitidine) are yellow, capsule-shaped tablets embossed with "ZANTAC 300" on one side and "Glaxo" on the other. They are available in bottles of 30 (NDC 0173-0393-40) and unit dose packs of 100 tablets (NDC 0173-0393-47).

ZANTAC® 150 Tablets (ranitidine hydrochloride equivalent to 150 mg of ranitidine) are white tablets embossed with "ZANTAC 150" on one side and "Glaxo" on the other. They are available in bottles of 60 tablets (NDC 0173-0344-42) and unit dose packs of 100 tablets (NDC 0173-0344-47).

Store between 15° and 30°C (59° and 86°F) in a dry place. Protect from fight. Replace cap securely after each opening.

August 1987

Glaxo

Glaxo Inc.
Research Triangle Park, NC 27709

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Books Received

Books received by THE WESTERN JOURNAL OF MEDICINE *are acknowledged in this column. Selections will be made for more extensive review in the interest of readers as space permits.*

THE AGE OF MIRACLES—MEDICINE AND SURGERY IN THE NINETEENTH CENTURY—Guy Williams. Academy Chicago Publishers, 425 N Michigan Ave, Chicago, IL 60611, 1987. 230 pages; $16.95 (clothbound), $8.95 (paperback).

CLINICAL DECISION LEVELS FOR LAB TESTS—Second Edition—Bernard E. Statland, MD, PhD, Medical Director and Department Head, Pathology and Laboratory Medicine, Methodist Hospital of Indiana, Indianapolis. Medical Economics Books, Oradell, NJ 07649, 1987. 221 pages, $21.95 (paperback).

CLINICAL IMAGING—AN INTRODUCTION TO THE ROLE OF IMAGING IN CLINICAL PRACTICE—Edited by Matthew Freedman, MD, Associate Professor of Diagnostic Radiology, Georgetown University School of Medicine; Associate Professor of Diagnostic Radiology, Johns Hopkins University School of Medicine; and Associate Professor of Diagnostic Radiology and Assistant Professor of Orthopedic Surgery, University of Maryland School of Medicine, Baltimore. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1988. 589 pages, $45.

COMMUNITY HEALTH AIDE/PRACTITIONER MANUAL—Robert D. Burgess, MD, Medical Director, Community Health Aide Program, Alaska Area Native Health Service, Anchorage. Alaska Native Health Service, 1345 Rudakof Circle, Suite 206, Anchorage, AK 99508, 1987. 449 pages, $34 (plus $3.50 postage and handling).

CONSOLIDATED STANDARDS SCORING GUIDELINES—PATIENT MANAGEMENT. Joint Commission on Accreditation of Healthcare Organizations, 875 N Michigan Ave, Chicago, IL 60611, 1988. 142 pages, $35 (paperback).

CRITICAL CARE OBSTETRICS—Edited by Steven L. Clark, MD, Director, Maternal-Fetal Medicine, Utah Valley Regional Perinatal Center, Provo; Jeffrey P. Phelan, MD, Associate Professor, Obstetrics and Gynecology, USC School of Medicine, Los Angeles; and David B. Cotton, MD, Associate Professor, Obstetrics and Gynecology, Baylor College of Medicine, Houston. Medical Economics Books, Oradell, NJ 07649, 1987. 496 pages, $52.95.

DESIGNING CLINICAL RESEARCH—AN EPIDEMIOLOGIC APPROACH—Edited by Stephen B. Hulley, MD, MPH, Professor of Epidemiology, Medicine, and Health Policy, and Steven R. Cummings, MD, Assistant Professor of Medicine and Epidemiology, University of California, San Francisco. Williams & Wilkins, 428 E Preston St, Baltimore, MD 21202, 1988. 236 pages, $19.95 (paperback).

A DIAGNOSTIC APPROACH TO CHEST DISEASES—DIFFERENTIAL DIAGNOSES BASED ON ROENTGENOGRAPHIC PATTERNS—Third Edition—Glen A. Lillington, MD, Chief, Division of Pulmonary and Critical Care Medicine, and Professor of Medicine, Department of Internal Medicine, University of California, Davis, School of Medicine. Williams & Wilkins, 428 E Preston St, Baltimore, MD 21202, 1987. 516 pages, $73.50.

DISEASES OF THE KIDNEY—Fourth Edition—3 volumes—Edited by Robert W. Schrier, MD, Professor and Chairman, Department of Medicine, and Head, Division of Renal Diseases, University of Colorado School of Medicine, Denver, and Carl W. Gottschalk, MD, Career Investigator, American Heart Association, and Kenan Professor of Medicine and Physiology, University of North Carolina School of Medicine, Chapel Hill. Little, Brown and Company, 34 Beacon St, Boston, MA 02108, 1987. 3,506 pages, $195.

FINE AFFERENT NERVE FIBERS AND PAIN—Edited by R. F. Schmidt, H.-G. Schaible, C. Vahle-Hinz. VCH Publishers, Inc, 220 E 23rd St, Suite 909, New York, NY 10010, 1987. 479 pages, $130.

FRACTIONAL ARTHROGRAPHY OF THE SHOULDER—Marc Rakofsky; translated from the French by Z. Stielle. VCH Publishers, Inc, 220 E 23rd St, Suite 909, New York, NY 10010, 1987. 224 pages, $85.

FRACTURE HEALING—Bristol-Myers/Zimmer Orthopaedic Symposium—Edited by Joseph M. Lane, MD, Professor of Orthopaedic Surgery, Cornell University Medical College; Chief, Orthopaedic Service, Memorial Sloan-Kettering Cancer Center; and Chief, Metabolic Bone Disease Unit, The Hospital for Special Surgery, New York. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1987. 275 pages, $45.

HOSPITAL ACCREDITATION PROGRAM SCORING GUIDELINES—NURSING SERVICES, INFECTION CONTROL, SPECIAL CARE UNITS. Joint Commission on Accreditation of Healthcare Organizations, 875 N Michigan Ave, Chicago, IL 60611, 1987. 57 pages, $35 (paperback).

THE LOVELACE MEDICAL CENTER—PIONEER IN AMERICAN HEALTH CARE—Jake W. Spidle, Jr, Professor of History, University of New Mexico, Albuquerque. University of New Mexico Press, Albuquerque, NM 87131, 1987. 209 pages, price not given.

MANAGING CONTRACEPTIVE PILL PATIENTS—Fifth Edition—Richard P. Dickey, MD, PhD, Clinical Associate Professor, Department of Obstetrics and Gynecology, Tulane University, and Director, Fertility Institute of New Orleans. Creative Infomatics, Inc, PO Box 1607, Durant, OK 74702-1607, 1987. 259 pages, price not given (paperback).

MANUAL FOR EYE EXAMINATION AND DIAGNOSIS—Third Edition—Mark W. Leitman, MD, Attending Physician, Robert Wood Johnson Hospital and St Peter's Medical Center, New Brunswick, New Jersey. Medical Economics Books, Oradell, NJ 07649, 1988. 80 pages, $18.95 (paperback).

MEDICAID AND PEDIATRIC PRIMARY CARE—Janet D. Perloff, Phillip R. Kletke, and Kathryn M. Neckerman. The Johns Hopkins University Press, 701 W 40th St, Suite 275, Baltimore, MD 21211, 1987. 184 pages, $30.

MEDICINE AND SOCIETY IN WAKEFIELD AND HUDDERSFIELD—1780-1870—Hilary Marland, Wellcome Unit for the History of Medicine, University of Oxford. Cambridge University Press, 32 E 57th St, New York, NY 10022, 1987. 485 pages, $59.50.

WYOMING MEDICAL SOCIETY

85th ANNUAL MEETING WMS HOUSE OF DELEGATES AND SCIENTIFIC SESSION
JUNE 23-25, 1988 • JACKSON LAKE LODGE, MORAN, WYOMING • GRAND TETON NATIONAL PARK

WMS ANNUAL MEETING AND SCIENTIFIC SESSION

LIFE AFTER MEDICAL SCHOOL—STAYING ALIVE AND VIABLE IN THE 1990s

THURSDAY, JUNE 23, 1988

8:00 AM REGISTRATION/EXHIBITS

9:00 AM WMS BOARD OF TRUSTEES

11:00 AM WMS HOUSE OF DELEGATES
OPENING SESSION
JOHN A. BARRASSO, MD
Speaker of the House of Delegates, Presiding

12 NOON Lunch (On Your Own)

1:15 PM Reference Committees
Afternoon Free

6:00 PM WELCOME TO THE TETONS SOCIAL HOUR
(Hosted by The Doctors' Company)

FRIDAY, JUNE 24, 1988

8:00 AM REGISTRATION/EXHIBITS

8:20 AM MEADE O. DAVIS III, MD
WMS President
Welcoming Remarks

8:30 AM OPENING SESSION
ROBERT ELIOT, MD
Is There Life After Medical School?

9:45 AM Coffee Break—Exhibit Area

10:00 AM CONCURRENT SCIENTIFIC SESSIONS (Pick One)
A ROGER DOZOIS, MD
Current Concepts in the Treatment of Peptic Ulcer Disease
B ROBERT FREEDMAN, MD
Treatment of Stress and Anxiety

11:00 AM CONCURRENT SCIENTIFIC SESSIONS (Pick One)
A COLONEL RICHARD M. SATAVA, MD
Wilderness Medical Perspectives of the Invasion of Grenada
B DAVID F. CROWDER, MD
WILLIAM P. BERLINER, MD
Essentials of General Office Surgery

12:30 PM Lunch (On Your Own)
Afternoon Free

6:00 PM WMS PRESIDENT'S RECEPTION AND BANQUET
THE HONORABLE DICK CHENEY
United States Congressman—*Keynote Speaker*
Special Presentations and Entertainment

SATURDAY, JUNE 25, 1988

8:00 AM REGISTRATION/COFFEE/EXHIBITS

8:20 AM MEADE O. DAVIS III, MD
WMS President
Introductory Remarks

8:30 AM CONCURRENT SCIENTIFIC SESSIONS (Pick One)
A ROBERT J. DAVIS II, MD
DAVID J. SCHWARTZ, MD
Current Concepts in the Diagnosis and Treatment of Hypercholesteremia
B GEORGE GREENBERG, MD
Physician/Patient Relationships—The Risk Management Perspective—Part 1

9:30 AM Coffee Break—Exhibit Area

9:45 AM CONCURRENT SCIENTIFIC SESSIONS (Pick One)
A PAUL D. MILLER, MD
Current Concepts in the Treatment of Post-Menopausal Osteoporosis
B GEORGE GREENBERG, MD
Physician/Patient Relationships—The Risk Management Perspective—Part 2

10:45 AM Coffee Break—Exhibit Area

11:00 AM CLOSING SESSION—POINT/COUNTERPOINT
Capping Medical Malpractice Damages: Panacea or Placebo; Can Limits Contain or Reduce Professional Liability Costs?
MODERATOR: WILLIAM F. DOWNES, JD
Medicolegal Update and Point/Counterpoint Introductions
POINT/COUNTERPOINT DEBATE
LEON BLUESTONE vs JAMES E. FITZGERALD, JD

12:30 PM Lunch (On Your Own)

1:30 PM WMS HOUSE OF DELEGATES • CLOSING SESSION

FACULTY

William F. Berliner, MD
Practicing General Surgeon
Las Vegas, Nevada

Leon Bluestone
The Doctors' Company
Santa Monica, California

David F. Crowder, MD
Clinical Associate Professor of Surgery
University of Wyoming School of Human Medicine
Gillette, Wyoming

Robert J. Davis II, MD
Clinical Associate Professor
University of Wyoming School of Human Medicine
Practicing Cardiologist
Internal Medicine Group
Cheyenne, Wyoming

William F. Downes, JD
Brown and Drew
Casper, Wyoming

Roger Dozois, MD
Professor of Surgery
Mayo School of Medicine
Rochester, Minnesota

Robert S. Eliot, MD, FACC
Director, Cardiovascular Institute
Swedish Medical Center
Denver, Colorado

James E. Fitzgerald, JD
Wyoming Trial Lawyers Association
Cheyenne, Wyoming

Robert Freedman, MD
Professor of Psychiatry and Pharmacology
University of Colorado
Denver, Colorado

George Greenberg, MD
Chairman, Claims Policy Committee
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Reno, Nevada

Paul D. Miller, MD
Associate Clinical Professor of Medicine and Psychiatry
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Colonel Richard M. Satava, MD
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Practicing Cardiologist
Internal Medicine Group
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WYOMING Medical Society

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Cheyenne, WY
82003-4009
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REGISTRATION FORM FOR PHYSICIANS ATTENDING THE WMS ANNUAL MEETING
JUNE 23-25, 1988 • JACKSON LAKE LODGE • MORAN, WYOMING

NAME _____ SPOUSE'S NAME _____
ADDRESS _____ ZIP _____
____ Registration Fee ($80 for members, $100 for nonmembers) . . . . . $ _____
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____ Auxiliary Luncheon tickets @ $10 per person . . . . . $ _____
TOTAL $ _____

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____ Send Jackson Lake Lodge reservation form and Grand Teton Park lodging information.

(Continued from Page 743)

SITUATION WANTED

ADMINISTRATION/MANAGEMENT for Health Care Practices; HMO; other related services. Health professional with multi backgrounds and experience in Health Care, now a law student. If have position—contact Dr Robert L. Burns, 2351 Bonita, Highland, CA 92346; (714) 864-7141 for résumé.

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INTERNAL MEDICINE PRACTICE FOR SALE. Beautiful small northern California town. Solo practice with ideal on-call arrangement. Reply Number 101, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

TUCSON PRACTICE AVAILABLE. At 76, after 40 years, Internal Medicine, I would like to quit. Furnished office. No strings attached, just care for patients and charts. J. K. Bennett, MD, CM, 1601 N. Tucson Blvd, Ste 11, Tucson, AZ 85716; (602) 795-2244.

FAMILY PRACTICES IN SAN DIEGO. Long established—doctors retiring. Various priced with low down payments. Other speciality practices available. C.B.I. (619) 283-7009.

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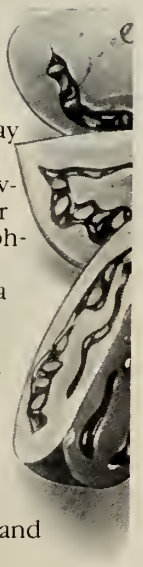

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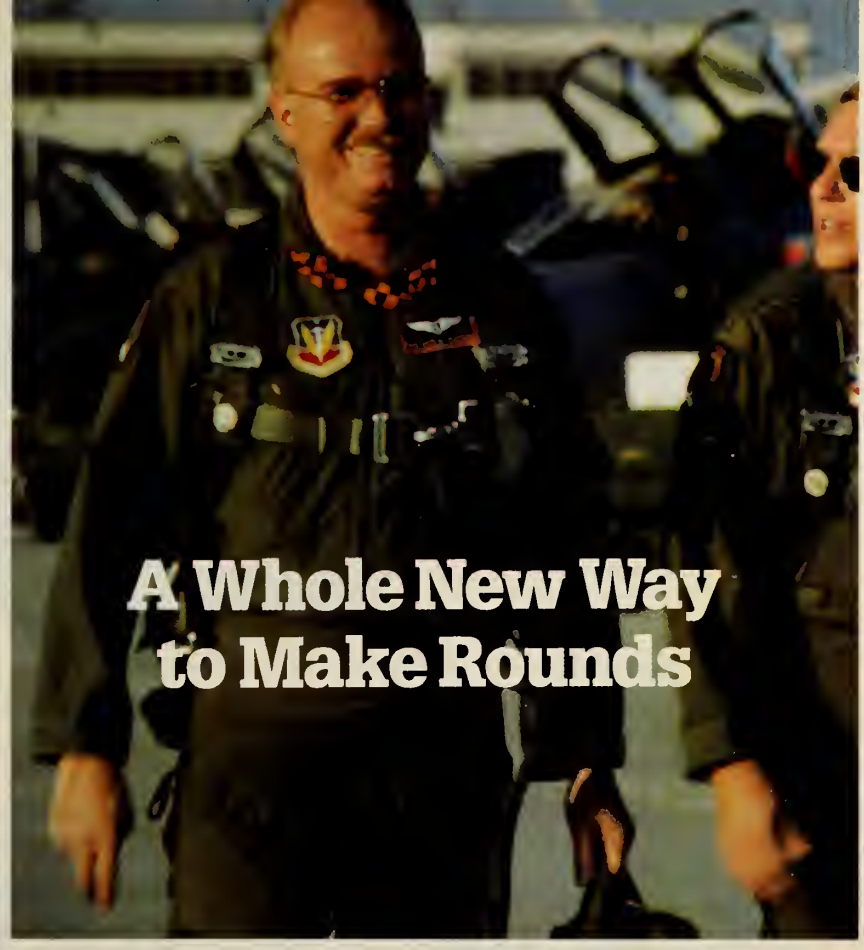

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Arizona Medical Association, Inc—810 W Bethany Home Rd, Phoenix 85013. (602) 246-8901. Annual Meeting: June 9-11, 1988, Loew's Ventana Canyon Resort, Tucson.

California Medical Association—PO Box 7690, San Francisco 94120-7690. (415) 541-0900. Annual Meeting: March 3-8, 1989, Disneyland Hotel, Anaheim.

Colorado Medical Society—PO Box 17550, Denver 80217-0550. (303) 779-5455. Annual Meeting: September 15-17, 1988, Marriott City Center, Denver.

Hawaii Medical Association—1360 S Beretania, Honolulu 96814. (808) 536-7702. Annual Meeting: October 10-12, 1987, Kauai Surf, Kauai.

Idaho Medical Association—305 W Jefferson, PO Box 2668, Boise 83701. (208) 344-7888. Annual Meeting: July 21-23, 1988, Sun Valley.

Montana Medical Association—2012 11th Ave, Suite 12, Helena 59601. (406) 443-4000. Annual Meeting: September 29-October 1, 1988, Heritage Inn, Great Falls.

Nevada State Medical Association—3660 Baker Lane, Reno 89502. (702) 825-6788. Annual Meeting: 1989, date and place to be announced.

New Mexico Medical Society—303 San Mateo NE, Suite 204, Albuquerque 87108. (505) 266-7868. Annual Meeting: 1989, date and place to be announced.

Oregon Medical Association—5210 SW Corbett Ave, Portland 97201. (503) 226-1555. Annual Meeting: (House of Delegates only): November 6-8, 1987, Portland.

Utah Medical Association—540 E Fifth South, Salt Lake City 84102. (801) 355-7477. Annual Meeting: September 21-23, 1988, University Park Hotel, Salt Lake City.

Washington State Medical Association—900 United Airlines Bldg, 2033 6th Ave, Seattle 98121. (206) 441-WSMA. Annual Meeting: September 15-18, 1988, Yakima.

Wyoming Medical Society—PO Drawer 4009, Cheyenne 82003-4009. (307) 635-2424. Annual Meeting: June 23-26, 1988, Jackson Lake Lodge, Moran.

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References: 1. Rubin RH, Swartz MN: *N Engl J Med 302*:426-432, Aug 21, 1980. 2. BAC-DATA Medical Information Systems, Inc., Volume I, 1986.

Bactrim™
(trimethoprim and sulfamethoxazole/Roche)

Before prescribing, please consult complete product information, a summary of which follows:
CONTRAINDICATIONS: Hypersensitivity to trimethoprim or sulfonamides; documented megaloblastic anemia due to folate deficiency; pregnancy at term and during the nursing period; infants less than two months of age.
WARNINGS: FATALITIES ASSOCIATED WITH THE ADMINISTRATION OF SULFONAMIDES, ALTHOUGH RARE, HAVE OCCURRED DUE TO SEVERE REACTIONS, INCLUDING STEVENS-JOHNSON SYNDROME, TOXIC EPIDERMAL NECROLYSIS, FULMINANT HEPATIC NECROSIS, AGRANULOCYTOSIS, APLASTIC ANEMIA AND OTHER BLOOD DYSCRASIAS.
BACTRIM SHOULD BE DISCONTINUED AT THE FIRST APPEARANCE OF SKIN RASH OR ANY SIGN OF ADVERSE REACTION. Clinical signs, such as rash, sore throat, fever, arthralgia, cough, shortness of breath, pallor, purpura or jaundice, may be early indications of serious reactions. In rare instances a skin rash may be followed by more severe reactions, such as Stevens-Johnson syndrome, toxic epidermal necrolysis, hepatic necrosis or serious blood disorder. Perform complete blood counts frequently.
BACTRIM SHOULD NOT BE USED IN THE TREATMENT OF STREPTOCOCCAL PHARYNGITIS. Clinical studies show that patients with group A β-hemolytic streptococcal tonsillopharyngitis have a greater incidence of bacteriologic failure when treated with Bactrim than with penicillin.
PRECAUTIONS: *General:* Give with caution to patients with impaired renal or hepatic function, possible folate deficiency (e.g., elderly, chronic alcoholics, patients on anticonvulsants, with malabsorption syndrome, or in malnutrition states) and severe allergies or bronchial asthma. In glucose-6-phosphate dehydrogenase deficient individuals, hemolysis may occur, frequently dose-related.
Use in the Elderly: May be increased risk of severe adverse reactions in elderly, particularly with complicating conditions, *e.g.*, impaired kidney and/or liver function, concomitant use of other drugs. Severe skin reactions, generalized bone marrow suppression (see WARNINGS and ADVERSE REACTIONS) or a specific decrease in platelets (with or without purpura) are most frequently reported severe adverse reactions in elderly. In those concurrently receiving certain diuretics, primarily thiazides, increased incidence of thrombocytopenia with purpura reported. Make appropriate dosage adjustments for patients with impaired kidney function (see DOSAGE AND ADMINISTRATION).
Use in the Treatment of Pneumocystis Carinii Pneumonia in Patients with Acquired Immunodeficiency Syndrome (AIDS): AIDS patients may not tolerate or respond to Bactrim in same manner as non-AIDS patients. Incidence of side effects, particularly rash, fever, leukopenia, elevated aminotransferase (transaminase) values, with Bactrim in AIDS patients treated for *Pneumocystis carinii* pneumonia reported to be greatly increased compared with incidence normally associated with Bactrim in non-AIDS patients.
Information for Patients: Instruct patients to maintain adequate fluid intake to prevent crystalluria and stone formation.
Laboratory Tests: Perform complete blood counts frequently; if a significant reduction in the count of any formed blood element is noted, discontinue Bactrim. Perform urinalyses with careful microscopic examination and renal function tests during therapy, particularly for patients with impaired renal function.
Drug Interactions: In elderly patients concurrently receiving certain diuretics, primarily thiazides, an increased incidence of thrombocytopenia with purpura has been reported. Bactrim may prolong the prothrombin time in patients who are receiving the anticoagulant warfarin. Keep this in mind when Bactrim is given to patients already on anticoagulant therapy and reassess coagulation time. Bactrim may inhibit the hepatic metabolism of phenytoin. Given at a common clinical dosage, it increased the phenytoin half-life by 39% and decreased the phenytoin metabolic clearance rate by 27%. When giving these drugs concurrently, be alert for possible excessive phenytoin effect. Sulfonamides can displace methotrexate from plasma protein binding sites, thus increasing free methotrexate concentrations.
Drug/Laboratory Test Interactions: Bactrim, specifically the trimethoprim component, can interfere with a serum methotrexate assay as determined by the competitive binding protein technique (CBPA) when a bacterial dihydrofolate reductase is used as the binding protein. No interference occurs if methotrexate is measured by a radioimmunoassay (RIA). The presence of trimethoprim and sulfamethoxazole may also interfere with the Jaffé alkaline picrate reaction assay for creatinine, resulting in overestimations of about 10% in the range of normal values.
Carcinogenesis, Mutagenesis, Impairment of Fertility: Carcinogenesis: Long-term studies in animals to evaluate carcinogenic potential not conducted with Bactrim. *Mutagenesis:* Bacterial mutagenic studies not performed with sulfamethoxazole and trimethoprim in combination. Trimethoprim demonstrated to be nonmutagenic in the Ames assay. No chromosomal damage observed in human leukocytes *in vitro* with sulfamethoxazole and trimethoprim alone or in combination; concentrations used exceeded blood levels of these compounds following therapy with Bactrim. Observations of leukocytes obtained from patients treated with Bactrim revealed no chromosomal abnormalities. *Impairment of Fertility:* No adverse effects on fertility or general reproductive performance observed in rats given oral dosages as high as 70 mg/kg/day trimethoprim plus 350 mg/kg/day sulfamethoxazole.
Pregnancy: Teratogenic Effects: Pregnancy Category C. Trimethoprim and sulfamethoxazole may interfere with folic acid metabolism; use during pregnancy only if potential benefit justifies potential risk to fetus. Nonteratogenic Effects: See CONTRAINDICATIONS section.
Nursing Mothers: See CONTRAINDICATIONS section.
Pediatric Use: Not recommended for infants under two months (see INDICATIONS and CONTRAINDICATIONS sections).
ADVERSE REACTIONS: Most common are gastrointestinal disturbances (nausea, vomiting, anorexia) and allergic skin reactions (such as rash and urticaria). **FATALITIES ASSOCIATED WITH THE ADMINISTRATION OF SULFONAMIDES, ALTHOUGH RARE, HAVE OCCURRED DUE TO SEVERE REACTIONS, INCLUDING STEVENS-JOHNSON SYNDROME, TOXIC EPIDERMAL NECROLYSIS, FULMINANT HEPATIC NECROSIS, AGRANULOCYTOSIS, APLASTIC ANEMIA AND OTHER BLOOD DYSCRASIAS (SEE WARNINGS SECTION).**
Hematologic: Agranulocytosis, aplastic anemia, thrombocytopenia, leukopenia, neutropenia, hemolytic anemia, megaloblastic anemia, hypoprothrombinemia, methemoglobinemia, eosinophilia. *Allergic Reactions:* Stevens-Johnson syndrome, toxic epidermal necrolysis, anaphylaxis, allergic myocarditis, erythema multiforme, exfoliative dermatitis, angioedema, drug fever, chills, Henoch-Schoenlein purpura, serum sickness-like syndrome, generalized allergic reactions, generalized skin eruptions, photosensitivity, conjunctival and scleral injection, pruritus, urticaria and rash. Periarteritis nodosa and systemic lupus erythematosus have been reported. *Gastrointestinal:* Hepatitis (including cholestatic jaundice and hepatic necrosis), elevation of serum transaminase and bilirubin, pseudomembranous enterocolitis, pancreatitis, stomatitis, glossitis, nausea, emesis, abdominal pain, diarrhea, anorexia. *Genitourinary:* Renal failure, interstitial nephritis, BUN and serum creatinine elevation, toxic nephrosis with oliguria and anuria, crystalluria. *Neurologic:* Aseptic meningitis, convulsions, peripheral neuritis, ataxia, vertigo, tinnitus, headache. *Psychiatric:* Hallucinations, depression, apathy, nervousness. *Endocrine:* Sulfonamides bear certain chemical similarities to some goitrogens, diuretics (acetazolamide and the thiazides) and oral hypoglycemic agents; cross-sensitivity may exist. Diuresis and hypoglycemia have occurred rarely in patients receiving sulfonamides. *Respiratory:* Pulmonary infiltrates. *Musculoskeletal:* Arthralgia, myalgia. *Miscellaneous:* Weakness, fatigue, insomnia.
DOSAGE AND ADMINISTRATION: Not recommended for use in infants less than two months of age.
URINARY TRACT INFECTIONS AND SHIGELLOSIS IN ADULTS AND CHILDREN, AND ACUTE OTITIS MEDIA IN CHILDREN: *Usual adult dosage* for urinary tract infections is one DS tablet, two tablets or four teaspoonfuls (20 ml) *b.i.d.* for 10 to 14 days. Use identical daily dosage for 5 days for shigellosis. *Recommended dosage for children* with urinary tract infections or acute otitis media is 8 mg/kg trimethoprim and 40 mg/kg sulfamethoxazole per 24 hours, in two divided doses every 12 hours for 10 days. Use identical daily dosage for 5 days for shigellosis. *Renal Impaired:* Creatinine clearance above 30 ml/min, give usual dosage; 15-30 ml/min, give one-half the usual regimen; below 15 ml/min, use not recommended.
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(160 mg trimethoprim and 800 mg sulfamethoxazole/Roche)

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